Pyrimidine Compounds as Purine Receptor Antagonists

The present invention relates to pyrimidine-4-carboxamide derivatives and their use in therapy. In particular, the present invention relates to the treatment of disorders in which the reduction of purinergic neurotransmission could be beneficial. The invention relates in particular to blockade of adenosine receptors and particularly adenosine A_{2A} receptors, and to the treatment of movement disorders such as Parkinson's disease.

Movement disorders constitute a serious health problem, especially amongst the elderly sector of the population. These movement disorders are often the result of brain lesions. Disorders involving the basal ganglia which result in movement disorders include Parkinson's disease, Huntington's chorea and Wilson's disease. Furthermore, dyskinesias often arise as sequelae of cerebral ischaemia and other neurological disorders.

There are four classic symptoms of Parkinson's disease: tremor, rigidity, akinesia and postural changes. The disease is also commonly associated with depression, dementia and overall cognitive decline. Parkinson's disease has a prevalence of 1 per 1,000 of the total population. The incidence increases to 1 per 100 for those aged over 60 years. Degeneration of dopaminergic neurones in the substantia nigra and the subsequent reductions in interstitial concentrations of dopamine in the striatum are critical to the development of Parkinson's disease. Some 80% of cells from the substantia nigra need to be destroyed before the clinical symptoms of Parkinson's disease are manifested.

Current strategies for the treatment of Parkinson's disease are based on transmitter replacement therapy (L-dihydroxyphenylacetic acid (L-DOPA)), inhibition of monoamine oxidase (e.g. Deprenyl®), dopamine receptor agonists (e.g. bromocriptine and apomorphine) and anticholinergics (e.g. benztrophine, orphenadrine). Transmitter replacement therapy in particular does not provide consistent clinical benefit, especially after prolonged treatment when "on-off" symptoms develop, and this treatment has also been associated with involuntary movements of athetosis and chorea, nausea and vomiting. Additionally current therapies do not treat the underlying neurodegenerative disorder resulting in a continuing cognitive decline in patients. Despite new drug approvals, there is still a medical need in terms of improved therapies for movement disorders, especially Parkinson's disease. In particular, effective treatments requiring less frequent dosing, effective treatments which are associated with less severe side-effects,

and effective treatments which control or reverse the underlying neurodegenerative disorder, are required.

Blockade of A_2 adenosine receptors has recently been implicated in the treatment of movement disorders such as Parkinson's disease (Richardson, P.J. *et al.*, *Trends Pharmacol. Sci.* 1997, 18, 338-344) and in the treatment of cerebral ischaemia (Gao, Y. and Phillis, J.W., *Life Sci.* 1994, 55, 61-65). The potential utility of adenosine A_{2A} receptor antagonists in the treatment of movement disorders such as Parkinson's Disease has recently been reviewed (Mally, J. and Stone, T.W., *CNS Drugs*, 1998, 10, 311-320).

Adenosine is a naturally occurring purine nucleoside which has a wide variety of well-documented regulatory functions and physiological effects. The central nervous system (CNS) effects of this endogenous nucleoside have attracted particular attention in drug discovery, owing to the therapeutic potential of purinergic agents in CNS disorders (Jacobson, K.A. *et al.*, *J. Med. Chem.* 1992, 35, 407-422). This therapeutic potential has resulted in considerable recent research endeavour within the field of adenosine receptor agonists and antagonists (Bhagwhat, S.S.; Williams, M. *Exp. Opin. Ther. Patents* 1995, 5,547-558).

Adenosine receptors represent a subclass (P_1) of the group of purine nucleotide and nucleoside receptors known as purinoreceptors. The main pharmacologically distinct adenosine receptor subtypes are known as A_1, A_{2A}, A_{2B} (of high and low affinity) and A_3 (Fredholm, B.B., *et al.*, *Pharmacol. Rev.* 1994, 46, 143-156). The adenosine receptors are present in the CNS (Fredholm, B.B., *News Physiol. Sci.*, 1995, 10, 122-128).

The design of P_1 receptor-mediated agents has been reviewed (Jacobson, K.A., Suzuki, F., *Drug Dev. Res.*, 1997, 39, 289-300; Baraldi, P.G. *et al.*, *Curr. Med. Chem.* 1995, 2, 707-722), and such compounds are claimed to be useful in the treatment of cerebral ischemia or neurodegenerative disorders, such as Parkinson's disease (Williams, M. and Burnstock, G. *Purinergic Approaches Exp. Ther.* (1997), 3-26. Editor: Jacobson, Kenneth A.; Jarvis, Michael F. Publisher: Wiley-Liss, New York, N.Y.)

It has been speculated that xanthine derivatives such as caffeine may offer a form of treatment for attention-deficit hyperactivity disorder (ADHD). A number of studies have demonstrated a beneficial effect of caffeine on controlling the symptoms of ADHD (Garfinkel, B.D. *et al., Psychiatry*, 1981, **26**, 395-401). Antagonism of adenosine receptors

is thought to account for the majority of the behavioural effects of caffeine in humans and thus blockade of adenosine A_{2A} receptors may account for the observed effects of caffeine in ADHD patients. Therefore a selective A_{2A} receptor antagonist may provide an effective treatment for ADHD but without the unwanted side-effects associated with current therapy.

Adenosine receptors have been recognised to play an important role in regulation of sleep patterns, and indeed adenosine antagonists such as caffeine exert potent stimulant effects and can be used to prolong wakefulness (Porkka-Heiskanen, T. *et al., Science,* 1997, **276**, 1265-1268). Recent evidence suggests that a substantial part of the actions of adenosine in regulating sleep is mediated through the adenosine A_{2A} receptor (Satoh, S., *et al., Proc. Natl. Acad. Sci.,* USA, 1996). Thus, a selective A_{2A} receptor antagonist may be of benefit in counteracting excessive sleepiness in sleep disorders such as hypersomnia or narcolepsy.

It has recently been observed that patients with major depression demonstrate a blunted response to adenosine agonist-induced stimulation in platelets, suggesting that a dysregulation of A_{2A} receptor function may occur during depression (Berk, M. et al, 2001, *Eur. Neuropsychopharmacol.* 11, 183-186). Experimental evidence in animal models has shown that blockade of A_{2A} receptor function confers antidepressant activity (El Yacoubi, M et al. *Br. J. Pharmacol.* 2001, 134, 68-77). Thus, A_{2A} receptor antagonists may offer a novel therapy for the treatment of major depression and other affective disorders in patients.

Also recently, from patent publication WO 2004/108137 (Kyowa Hakko Kogyo), it is now considered that adenosine A_{2A} receptor antagonists are useful in the treatment of anxiety disorders, including panic disorder, agorophobia, obsessive compulsive disorder, social phobia, post traumatic stress disorder, generalised anxiety disorder and specific phobia.

The pharmacology of adenosine A_{2A} receptors has been reviewed (Ongini, E.; Fredholm, B.B. *Trends Pharmacol. Sci.* 1996, 17(10), 364-372). One potential underlying mechanism in the aforementioned treatment of movement disorders by the blockade of A_2 adenosine receptors is the evidence of a functional link between adenosine A_{2A} receptors to dopamine D_2 receptors in the CNS. Some of the early studies (e.g. Ferre, S. *et al.*, Stimulation of high-affinity adenosine A_2 receptors decreases the affinity of dopamine D_2 receptors in rat striatal membranes. *Proc. Natl. Acad. Sci.* U.S.A. 1991, 88, 7238-41)

have been summarised in two more recent articles (Fuxe, K. *et al., Adenosine Adenine Nucleotides Mol. Biol. Integr. Physiol.*, [Proc. Int. Symp.], 5th (1995), 499-507. Editors: Belardinelli, Luiz; Pelleg, Amir. Publisher: Kluwer, Boston, Mass.; Ferre, S. *et al.*, *Trends Neurosci.* 1997, 20, 482-487).

As a result of these investigations into the functional role of adenosine A_{2A} receptors in the CNS, especially *in vivo* studies linking A_2 receptors with catalepsy (Ferre *et al.*, *Neurosci. Lett.* 1991, 130, 162-4; Mandhane, S.N. *et al.*, *Eur. J. Pharmacol.* 1997, 328, 135-141) investigations have been made into agents which selectively bind to adenosine A_{2A} receptors as potentially effective treatments for Parkinson's disease.

While many of the potential drugs for treatment of Parkinson's disease have shown benefit in the treatment of movement disorders, an advantage of adenosine A_{2A} antagonist therapy is that the underlying neurodegenerative disorder may also be treated. The neuroprotective effect of adenosine A_{2A} antagonists has been reviewed (Ongini, E.; Adami, M.; Ferri, C.; Bertorelli, R., *Ann. N. Y. Acad. Sci.* 1997, 825(Neuroprotective Agents), 30-48). In particular, compelling recent evidence suggests that blockade of A_{2A} receptor function confers neuroprotection against MPTP-induced neurotoxicity in mice (Chen, J-F., *J. Neurosci.* 2001, 21, RC143). In addition, several recent studies have shown that consumption of dietary caffeine, a known adenosine A_{2A} receptor antagonist, is associated with a reduced risk of Parkinson's disease in man (Ascherio, A. et al, *Ann Neurol.*, 2001, 50, 56-63; Ross G W, et al., *JAMA*, 2000, 283, 2674-9). Thus, A_{2A} receptor antagonists may offer a novel treatment for conferring neuroprotection in neurodegenerative diseases such as Parkinson's disease.

Xanthine derivatives have been disclosed as adenosine A_2 receptor antagonists as useful for treating various diseases caused by hyperfunctioning of adenosine A_2 receptors, such as Parkinson's disease (see, for example, EP-A-565377).

One prominent xanthine-derived adenosine A_{2A} selective antagonist is CSC [8-(3-chlorostyryl)caffeine] (Jacobson *et al.*, *FEBS Lett.*, 1993, 323, 141-144).

Theophylline (1,3-dimethylxanthine), a bronchodilator drug which is a mixed antagonist at adenosine A_1 and A_{2A} receptors, has been studied clinically. To determine whether a formulation of this adenosine receptor antagonist would be of value in Parkinson's disease an open trial was conducted on 15 Parkinsonian patients, treated for up to 12 weeks with

a slow release oral theophylline preparation (150 mg/day), yielding serum theophylline levels of 4.44 mg/L after one week. The patients exhibited significant improvements in mean objective disability scores and 11 reported moderate or marked subjective improvement (Mally, J., Stone, T.W. *J. Pharm. Pharmacol.* 1994, 46, 515-517).

KF 17837 [(E)-8-(3,4-dimethoxystyryl)-1,3-dipropyl-7-methylxanthine] is a selective adenosine A_{2A} receptor antagonist which on oral administration significantly ameliorated the cataleptic responses induced by intracerebroventricular administration of an adenosine A_{2A} receptor agonist, CGS 21680. KF 17837 also reduced the catalepsy induced by haloperidol and reserpine. Moreover, KF 17837 potentiated the anticataleptic effects of a subthreshold dose of L-DOPA plus benserazide, suggesting that KF 17837 is a centrally active adenosine A_{2A} receptor antagonist and that the dopaminergic function of the nigrostriatal pathway is potentiated by adenosine A_{2A} receptor antagonists (Kanda, T. *et al.*, *Eur. J. Pharmacol.* 1994, 256, 263-268). The structure activity relationship (SAR) of KF 17837 has been published (Shimada, J. *et al.*, *Bioorg. Med. Chem. Lett.* 1997, 7, 2349-2352). Recent data has also been provided on the A_{2A} receptor antagonist KW-6002 (Kuwana, Y *et al.*, *Soc. Neurosci. Abstr.* 1997, 23, 119.14; and Kanda, T. *et al.*, *Ann. Neurol.* 1998, 43(4), 507-513).

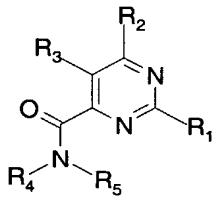
New non-xanthine structures sharing these pharmacological properties include SCH 58261 and its derivatives (Baraldi, P.G. *et al.*, Pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine Derivatives: Potent and Selective A_{2A} Adenosine Antagonists. *J. Med. Chem.* 1996, 39, 1164-71). SCH 58261 (7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-e]-1,2,4-triazolo[1,5-c] pyrimidine) is reported as effective in the treatment of movement disorders (Ongini, E. *Drug Dev. Res.* 1997, 42(2), 63-70) and has been followed up by a later series of compounds (Baraldi, P.G. *et al.*, *J. Med. Chem.* 1998, 41(12), 2126-2133). WO-A-01/62233 discloses a series of cyclic heteroaromatic compounds containing at least one nitrogen atom and their use as adenosine receptor modulators. FR-2201083 discloses a series of phenylpyrimidines with analgesic activity.

The foregoing discussion indicates that a potentially effective treatment for movement disorders in humans would comprise agents which act as antagonists at adenosine A_{2A} receptors.

It has now been found that the pyrimidine-4-carboxamide derivatives described herein, which are structurally unrelated to known adenosine receptor antagonists, exhibit

unexpected antagonist binding affinity at adenosine (P_1) receptors, and in particular at the adenosine A_{2A} receptor. Such compounds may therefore be useful for the treatment of disorders in which the blocking of purine receptors, particularly adenosine receptors and more particularly adenosine A_{2A} receptors, is beneficial, for instance movement disorders, such as disorders of the basal ganglia which result in dyskinesias.

According to the present invention there is provided the use of a compound of formula (1):



(I)

wherein

R_1 is optionally substituted C_1-C_6alkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl, or -NR_6R_7, -OR_8, -SR_9 or halogen;

R_2 is optionally substituted aryl or heteroaryl attached via a carbon atom;

R_3 is H; optionally substituted C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_7 cycloalkyl, halogen; OH or OR_{10};

R_4 is H, optionally substituted C_1-C_6alkyl, C_3-C_6alkenyl, C_3-C_6alkynyl, C_3-C_7 cycloalkyl, aryl or heteroaryl,

R_5 is H or optionally substituted C_1-C_6alkyl, C_3-C_6alkenyl, C_3-C_6alkynyl, or C_3-C_7 cycloalkyl; or R_4 and R_5 together form a 5 or 6-membered heterocyclic ring;

R_6 is H or optionally substituted C_1-C_3alkyl, C_3-C_6alkenyl, C_3-C_6alkynyl, or C_3-C_7 cycloalkyl;

R_7, R_8, R_9 and R_{10} are optionally substituted C_1-C_3alkyl, C_3-C_6alkenyl, C_3-C_6alkynyl, or C_3-C_7 cycloalkyl

or R_6 and R_7 together form a 5 or 6-membered heterocyclic ring;

and pharmaceutically acceptable salts and prodrugs thereof, in the manufacture of a medicament for the treatment or prevention of a disorder in which the blocking of purine receptors is beneficial.

The class of compounds (I) with which the invention is concerned are antagonists of the A_{2A} receptor, and in many cases are selective antagonists of the A_{2A} receptor over the other adenosine receptor subtypes described herein.

As used herein the term "carboxamide group" refers to a group of formula -$CONR_aR_b$, wherein -NR_aR_b is an amino (including cyclic amino) group actually or notionally derived from ammonia or the amine HNR_aR_b.

As used herein, the term "(C_a-C_b)alkyl" wherein a and b are integers refers to a straight or branched chain alkyl radical having from a to b carbon atoms. Thus when a is 1 and b is 6, for example, the term includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein the term "(C_a-C_b)alkenyl" wherein a and b are integers refers to a straight or branched chain alkenyl moiety having from a to b carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. The term includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "cycloalkyl" refers to a saturated carbocyclic radical having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "cycloalkenyl" refers to a carbocyclic radical having from 3-8 carbon atoms containing at least one double bond, and includes, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

As used herein the term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic radical and includes mono or bicyclic aromatic rings fused to a cycloalkyl ring. Illustrative of such radicals are phenyl, biphenyl and napthyl.

As used herein the term "carbocyclic" refers to a cyclic radical whose ring atoms are all carbon, and includes monocyclic aryl, cycloalkyl, and cycloalkenyl radicals.

As used herein the term "heteroaryl" refers to a mono-, bi- or tri-cyclic aromatic radical containing one or more heteroatoms selected from S, N and O, and includes mono or bicyclic of the foregoing type fused to a cycloalkyl ring. Illustrative of such radicals are thienyl, benzthienyl, furyl, benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl, benzisothiazolyl, pyrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolyl and indazolyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in particular refers to a mono-, bi- or tri-cyclic non-aromatic radical containing one or more heteroatoms selected from S, N and O, and to groups consisting of a monocyclic non-aromatic radical containing one or more such heteroatoms which is covalently linked to another such radical or to a monocyclic carbocyclic radical. Illustrative of such radicals are pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzfuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, maleimido and succinimido groups.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with at least one substituent, for example selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, hydroxy(C_1-C_6)alkyl, mercapto, mercapto(C_1-C_6)alkyl, (C_1-C_6)alkylthio, halo (including fluoro and chloro), trifluoromethyl, trifluoromethoxy, nitro, nitrile (-CN), oxo, phenyl, monocyclic heterocyclic having 5- or 6 ring members, -COOH, -$COOR^A$, -COR^A, -SO_2R^A, -$CONH_2$, -SO_2NH_2, -$CONHR^A$, -SO_2NHR^A, -$CONR^AR^B$, -$SO_2NR^AR^B$, -NH_2, -NHR^A, -NR^AR^B, -$OCONH_2$, -$OCONHR^A$, -$OCONR^AR^B$, -$NHCOR^A$, -NR^BCOR^A, -$NHCOOR^A$, -NR^BCOOR^A, -$NHSO_2R^A$, -$NR^BSO_2R^A$, -$NHCONH_2$, -NR^ACONH_2, -$NHCONHR^B$, -NR^ACONHR^B, -$NHCONR^AR^B$, or -$NR^ACONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl group. An “optional substituent” may be one of the foregoing substituent groups. Where the optional substituent is phenyl, monocyclic heterocyclic having 5- or 6 ring members, then it too may be substituted by any of the foregoing except phenyl and monocyclic heterocyclic having 5- or 6 ring members.

As used herein the term “salt” includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically or veterinarily acceptable salts, with bases such as alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-ethyl piperidine, dibenzylamine and the like. Those compounds (I) which are basic can form salts, including pharmaceutically or veterinarily acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic and p-toluene sulphonic acids and the like.

For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Compounds with which the invention is concerned which may exist in one or more stereoisomeric form, because of the presence of asymmetric atoms or rotational restrictions, can exist as a number of stereoisomers with R or S stereochemistry at each chiral centre or as atropisomeres with R or S stereochemistry at each chiral axis. The invention includes all such enantiomers and diastereoisomers and mixtures thereof

So-called 'pro-drugs' of the compounds of formula (I) are also within the scope of the invention. Thus certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

Also included within the scope of the invention are metabolites of compounds of formula (I), that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites include

(i) where the compound of formula (I) contains a methyl group, an hydroxymethyl derivative thereof ($-CH_3$ -> $-CH_2OH$):

(ii) where the compound of formula (I) contains an alkoxy group, an hydroxy derivative thereof (-OR -> -OH);

(iii) where the compound of formula (I) contains a tertiary amino group, a secondary amino derivative thereof ($-NR^1R^2$ -> $-NHR^1$ or $-NHR^2$);

(iv) where the compound of formula (I) contains a secondary amino group, a primary derivative thereof ($-NHR^1$ -> $-NH_2$);

(v) where the compound of formula (I) contains a phenyl moiety, a phenol derivative thereof (-Ph -> -PhOH); and

(vi) where the compound of formula (I) contains an amide group, a carboxylic acid derivative thereof ($-CONH_2$ -> COOH).

The group R_1

One subset of groups R_1 comprises halogen, optionally substituted C_1-C_3alkyl or C_2-C_3alkenyl, and $-NR_6R_7$, $-OR_8$, $-SR_9$ wherein R_6 is H or optionally substituted C_1-C_3alkyl, and R_7, R_8, and R_9 are C_1-C_3alkyl. Specific examples of groups R_1 are methyl, ethyl, n- or iso-propyl, trifuoromethyl, allyl, cyclopropyl, chloro, bromo or fluoro. Further specific examples of R_1 groups are $-NR_6R_7$, $-OR_8$, $-SR_9$ wherein R_6 is hydrogen, methyl, ethyl, n- or iso-propyl, ,or allyl; R_7 is methyl, ethyl, n- or iso-propyl, or allyl; R_8 and R_9 are methyl, ethyl, n- or iso-propyl, trifuoromethyl,or allyl, Presently preferred groups R_1 include - $NHCH_3$. R_6 and R_7 together may form a 5 or 6-membered heterocyclic ring, such as a piperidinyl, piperazinyl, morpholino and thiomorpholino.

The group R_2

In the compounds in accordance with the invention, R_2 is selected from aryl and heteroaryl attached via a carbon atom, including substituted aryl and heteroaryl. For example, R_2 may be optionally substituted phenyl or an optionally substituted monocyclic or bicyclic heteroaryl group such as optionally substituted furyl, thienyl, thiazolyl, oxazolyl, imidazolyl, pyridyl, indolyl or benzofuranyl. At present optionally substituted phenyl, furyl (preferably 2-furyl) and thiazolyl (preferably 2-thiazolyl) are preferred. Optional substituents which may be present in R_2 include C_1-C_3 alkyl such as methyl and ethyl, C_1-C_3 alkoxy such as methoxy and ethoxy, chloro, bromo, fluoro, trifluoromethyl, and carboxamide groups such as $-CONR^AR^B$ where R^A and R^B are independently hydrogen or C_1-C_3 alkyl. Where

optional substituents are present in monocyclic R_2, mono or disubstitution are presently preferred, although of the disubstitution options ortho-ortho disubstitution is less preferred at present. Examples of particular R_2 groups are 2-furyl, 5-methyl-2 furyl, 2-thiazolyl, 4-methyl-2-thiazolyl, phenyl, and o-methyl-phenyl.

The group R_3

In the compounds in accordance with the invention, R_3 is H; optionally substituted C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_7 cycloalkyl, halogen; OH or OR_{10} wherein R_{10} is optionally substituted C_1-C_6alkyl such as ethyl, methyl, or n-or iso-propyl. Presently it is preferred that R_3 is H, C_1-C_6alkyl, C_3-C_6 cycloalkyl, halo substituted C_1-C_6alkyl, or halogen. Specific R_3 groups include H, methyl, ethyl, n- and isopropyl, cyclopropyl, n-sec and tert-butyl, trifloromethyl, chloro, bromo and fluoro, and of the foregoing, hydrogen, methyl, chloro and bromo are presently preferred.

The group R_4

In the compounds in accordance with the invention, R_4 is H, optionally substituted C_1-C_6alkyl, C_3-C_6alkenyl, C_3-C_6alkynyl, C_3-C_7 cycloalkyl, aryl or heteroaryl, or together with R_5 forms a 5 or 6-membered heterocyclic ring.

Where R_4 is heteroaryl or includes a heteroaryl ring (for example where R_4 is heteroaryl(C_1-C_6alkyl)-), such rings include optionally substituted pyridyl, furanyl, thienyl, isoxazolyl, thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, benzimidazolyl, indolyl, benzthiazolyl, benzthiadiazolyl, quinolyl, and isoquinolyl. Of the foregoing, optionally substituted pyridyl (especially 2-pyridyl), imidazolyl, pyrazolyl, and isoxazolyl are most preferred at present.

Presently it is preferred that R_4 be C_1-C_6alkyl, substituted by aryl or heteroaryl, with the aryl or heteroaryl ring itself being optionally substituted. Within this category of R_4 groups are included arylmethyl and heteroarylmethyl, again with optional substitution in the aryl and heteroaryl rings. Phenyl is a preferred aryl ring, and heteroaryl rings in this category of R_4 groups include those listed in the preceding paragraph.

As indicated above, an aryl or heteroaryl group constituting or present in R_4 may be optionally substituted. Typically, only one substituent group is present. Optional substituents in this context include any of those referred to herein including C_1-C_3 alkyl such as methyl and ethyl, C_1-C_3 alkoxy such as methoxy and ethoxy, chloro, bromo, fluoro, trifluoromethyl, amino groups such as -NR^AR^B, carboxamide groups such as

-$CONR^AR^B$ and reverse carboxamide groups such as -NR^ACOR^B where R^A and R^B are independently hydrogen or C_1-C_3 alkyl or together form a 5 or 6-membered heterocyclic ring wherein said heterocyclic ring may be saturated, partially unsaturated or aromatic, and is preferably saturated, and wherein said heterocyclic ring may contain one or more additional heteroatom(s) preferably selected from N, O and S, and in one embodiment contains no further heteroatoms, and in one embodiment is unsubstituted.

The group R_5

In the compounds in accordance with the invention, R_5 is H or optionally substituted C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_7 cycloalkyl, or together with R_4 forms a 5 or 6-membered heterocyclic ring. Presently it is preferred that R_5 is hydrogen.

The groups R_4 and R_5 together

In the compounds in accordance with the invention, R_4 and R_5 may be linked to form a 5 or 6-membered heterocyclic ring, said heterocyclic ring may be saturated, partially unsaturated or aromatic, and is preferably saturated. Said heterocyclic ring may contain one or more additional heteroatom(s) preferably selected from N, O and S. In one embodiment, the heterocyclic ring contains no further heteroatoms, and in another the ring contains further heteroatoms as, for example, in morpholino, thiomorpholino, piperazino and piperazinyl substituted with, for example, C_1-C_3 alkyl on the second ring nitrogen. In one embodiment, the heterocyclic ring is unsubstituted. In one embodiment, the 5 or 6-membered heterocyclic ring may be fused to an aromatic ring system, particularly a monocyclic ring system (preferably containing 6 ring atoms, such as phenyl) to form a multicyclic moiety, such as dihydroindolyl, dihydroisoindolyl, tetrahydroquinolinyl or tetrahydroisoquinolinyl.

Where chiral the compounds of formula (I) may be in the form of a racemic mixture of pairs of enantiomers or in enantiomerically pure form.

According to a further aspect of the present invention there is provided a method of treating or preventing a disorder in which the blocking of purine receptors, particularly adenosine receptors and more particularly adenosine A_{2A} receptors, is beneficial, the method comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt or prodrug thereof.

The disorder with which the use or method of the invention is concerned may be caused by the hyperfunctioning of the purine receptors.

The use or method of the invention may be employed in respect of a human or animal subject, more preferably a mammal, more preferably a human subject.

The disorders of particular interest in connection with the use or method of the invention is concerned are those in which the blocking of purine receptors, particularly adenosine receptors and more particularly adenosine A_{2A} receptors, may be beneficial. These may include movement disorders such as Parkinson's disease, drug-induced Parkinsonism, post-encephalitic Parkinsonism, Parkinsonism induced by poisoning (for example MPTP, manganese, carbon monoxide) and post-traumatic Parkinson's disease (punch-drunk syndrome).

Other movement disorders in which the blocking of purine receptors, may be of benefit include progressive supernuclear palsy, Huntingtons disease, multiple system atrophy, corticobasal degeneration, Wilsons disease, Hallerrorden-Spatz disease, progressive pallidal atrophy, Dopa-responsive dystonia-Parkinsonism, spasticity or other disorders of the basal ganglia which result in abnormal movement or posture. The present invention may also be effective in treating Parkinson's with on-off phenomena; Parkinson's with freezing (end of dose deterioration); and Parkinson's with prominent dyskinesias.

Thus, according to a further aspect of the present invention, there is provided use of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for the treatment or prevention of movement disorders in a subject.

According to a further aspect of the invention there is provided a method of treating or preventing movement disorders comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof.

The compounds of formula (I) may be used or administered in combination with one or more additional drugs useful in the treatment of movement disorders, such as L-DOPA or a dopamine agonist, the components being in the same formulation or in separate formulations for administration simultaneously or sequentially.

Other disorders in which the blocking of purine receptors, particularly adenosine receptors and more particularly adenosine A_{2A} receptors may be beneficial include anxiety disorders, including panic disorder, agorophobia, obsessive compulsive disorder, social phobia, post traumatic stress disorder, generalised anxiety disorder and specific phobia.

The use and method of treatment of the invention is also applicable in the case of acute or chronic pain, for example non-inflammatory pain, particulary neuropathic pain, including trigeminal neuralgia, phantom limb pain, spinal cord injury pain, post-herpetic pain and HIV pain.

The use and method of the invention may also be useful in the case of affective disorders including mood disorders such as bipolar disorder, seasonal affective disorder, depression, manic depression, atypical depression and monodepressive disease; central and peripheral nervous system degenerative disorders including corticobasal degeneration, demyelinating disease (multiple sclerosis, disseminated sclerosis), Freidrich's ataxia, motoneurone disease (amyotrophic lateral sclerosis, progressive bulbar atrophy), multiple system atrophy, myelopathy, radiculopathy, peripheral neuropathy (diabetic neuropathy, tabes dorsalis, drug-induced neuropathy, vitamin deficiency), systemic lupus erythamatosis, granulomatous disease, olivo-ponto-cerebellar atrophy, progressive pallidal atrophy, progressive supranuclear palsy, spasticity; schizophrenia and related psychoses; cognitive and/or memory impairment disorders including dementia, Alzheimers Disease, Frontotemporal dementia, multi-infarct dementia, AIDS dementia, dementia associated with Huntingtons Disease, Lewy body dementia, senile dementia, age-related memory impairment, cognitive impairment associated with dementia, Korsakoff syndrome, dementia pugilans; attention disorders such as attention-deficit hyperactivity disorder (ADHD), attention deficit disorder, minimal brain dysfunction, brain-injured child syndrome, hyperkinetic reaction childhood, and hyperactive child syndrome; central nervous system injury including traumatic brain injury, neurosurgery (surgical trauma), neuroprotection for head injury, raised intracranial pressure, cerebral oedema, hydrocephalus, spinal cord injury; cerebral ischaemia including transient ischaemic attack, stroke (thrombotic stroke, ischaemic stroke, embolic stroke, haemorrhagic stroke, lacunar stroke) subarachnoid haemorrhage, cerebral vasospasm, neuroprotection for stroke, peri-natal asphyxia, drowning, cardiac arrest, subdural haematoma; myocardial ischaemia; muscle ischaemia; sleep disorders such as hypersomnia, narcolepsy and restless legs

syndrome; eye disorders such as retinal ischaemia-reperfusion injury and diabetic neuropathy; cardiovascular disorders such as claudication and hypotension; and diabetes and its complications.

According to a further aspect of the invention there is provided use of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for neuroprotection in a subject.

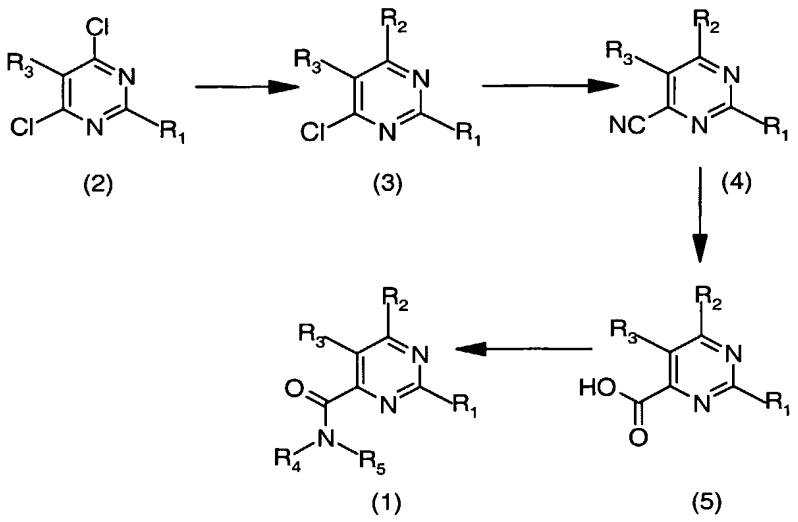
According to a further aspect of the invention there is provided a method of neuroprotection comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof.

The medicament for or method of neuroprotection may be of use in the treatment of subjects who are suffering from or at risk from a neurodegenerative disorder, such as a movement disorder.

The present invention also includes novel compounds forming a subset of the compounds of formula (I) as defined above, namely those wherein R_2 is optionally substituted 5-membered heteroaryl. In this subset, R_2 may be any of the optionally substituted 5-membered heteroaryl ring systems as discussed above, including the preferred and specific classes and examples of those ring systems.

There are multiple synthetic strategies for the synthesis of the compounds (I) with which the present invention is concerned, but all rely on known chemistry, known to the synthetic organic chemist. Thus, compounds according to formula (I) can be synthesised according to procedures described in the standard literature and are well-known to the one skilled in the art. Typical literature sources are "*Advanced organic chemistry*", 4th Edition (Wiley), J March, "*Comprehensive Organic Transformation*", 2nd Edition (Wiley), R.C. Larock , "*Handbook of Heterocyclic Chemistry*", 2nd Edition (Pergamon), A.R. Katritzky), review articles such as found in "*Synthesis*", "*Acc. Chem. Res.*" , "*Chem. Rev*", or primary literature sources identified by standard literature searches online or from secondary sources such as "*Chemical Abstracts*" or "*Beilstein*". Suitable reaction schemes are as follows.

Reaction Scheme 1



Compounds of formula (1) may be prepared from compounds of formula (5) by standard methods used for coupling carboxylic acids and amines. Such coupling reactions would include reaction of a carboxylic acid derivative such as an imidazolide prepared with N,N'-carbonyldiimidazole or a mixed anhydride prepared with an alkyl chloroformate and a trialkylamine base or an acyl chloride prepared from a chlorinating source such as oxalyl chloride with an appropriate amine, or by direct coupling of an appropriate amine in the presence of a standard coupling reagent such as dicyclohexylcarbodiimide and a nucleophilic catalyst such as 4-dimethylaminopyridine.

Compounds of formula (5) may be prepared from compounds of formula (4) by standard methods such as hydrolysis with a mineral acid such as sulfuric or hydrochloric acid.

Compounds of formula (4) may be prepared from compounds of formula (3) by standard methods such as cyanation with an alkali metal cyanide such as sodium cyanide or an organic source of cyanide such as tetraethylammonium cyanide in the presence of a tertiary amine base such as 1,4-diazabicyclo[2.2.2]octane or triethylamine.

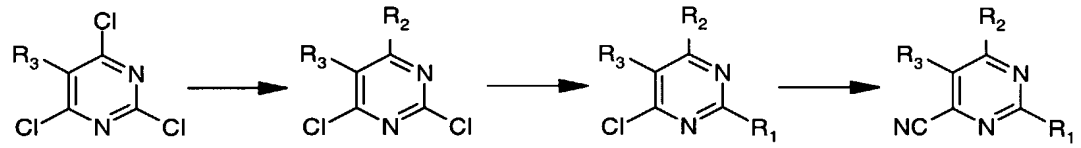
Compounds of formula (3) are either known in the literature or may be prepared from compounds of formula (2) by standard methods such as aryl or heteroaryl coupling reactions. Such aryl or heteroaryl coupling reactions would include reaction with an appropriate aryl or heteroarylboronic acid derivative, an aryl or heteroaryltrialkylstannane derivative or an aryl or heteroarylzinc halide derivative in the presence of a suitable catalyst such as a palladium complex.

Compounds of formula (2) are either known in the literature or may be prepared by standard methods.

In Reaction Scheme (1) compounds of formula (1), where R_3 is halogen, may be prepared from compounds of formula (1), where R_3 is H, by standard methods such as halogenation with N-bromo- or N-chlorosuccinnimide.

Compounds of formula (4), where R_1 is NR_6R_7, OR_8 or SR_9, may alternatively be synthesised by standard methods such as those illustrated in Reaction Scheme 2.

Reaction Scheme 2



(6) (7) (8) (4)

In Reaction Scheme (2) compounds of formula (4), where R_1 is NR_6R_7, OR_8 or SR_9, may be prepared from compounds of formula (8), where R_1 is NR_6R_7, OR_8 or SR_9, by standard methods such as cyanation as described above.

Compounds of formula (8), where R_1 is NR_6R_7, OR_8 or SR_9, may be prepared from compounds of formula (7), where R_1 is NR_6R_7, OR_8 or SR_9, by standard methods such as nucleophilic displacement with an amine (HNR_6R_7), alcohol (HOR_8) or thiol (HSR_9), optionally in the presence of a suitable base or alternatively by using preformed alkoxide or thiolate salt solutions.

Compounds of formula (7) may be prepared from compounds of formula (6) by standard methods such as aryl or heteroaryl coupling reactions as described above.

Compounds of formula (6) are either known in the literature or may be prepared by standard methods.

Compounds with which the invention is concerned may be presented in a pharmaceutical composition comprising a compound of formula (I) as defined and discussed above in combination with a pharmaceutically acceptable carrier or excipient.

Any suitable route of administration may be employed for providing the patient with an effective dosage of a compound of formula (I). For example, oral, rectal, parenteral (intravenous, intramuscular), transdermal, subcutaneous, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, and the like. The most suitable route in any given case will depend on the severity of the condition being treated. The most preferred route of administration of the present invention is the oral route. The compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practical use, the compounds of formula (I) can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, *e.g.* oral or parenteral (*e.g.* intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavouring agents, preservatives, colouring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used in the case of oral solid preparations such as, for example, powders, capsules, and tablets, with the solid oral preparations being preferred over the liquid preparations. The most preferred solid oral preparation is tablets.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or non-aqueous techniques.

In addition to the common dosage forms set out above, the compounds of formula (I) may also be administered by controlled release means and/or delivery devices such as those described in United States Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200; 4,008,719; 4,687,660; and 4,769,027, the disclosures of which are hereby incorporated by reference.

Pharmaceutical compositions employed in the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets,

or aerosol sprays each containing a predetermined amount of the active ingredient as a powder or granules, a solution or a suspension in an aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

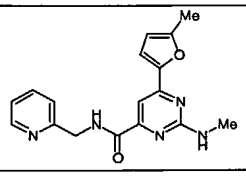
The invention is further defined by reference to the following examples. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practised without departing from the purpose and interest of this invention.

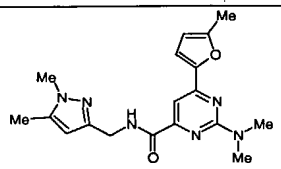
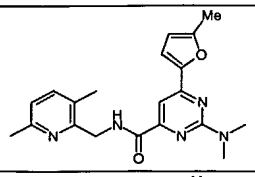
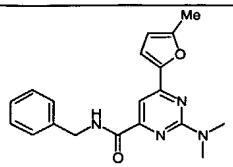
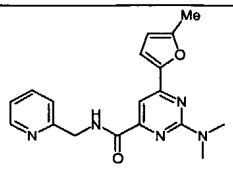
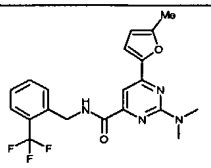
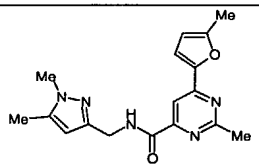
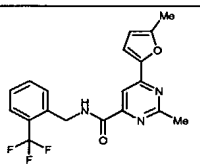
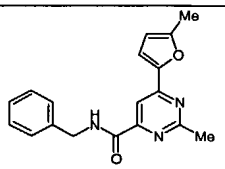
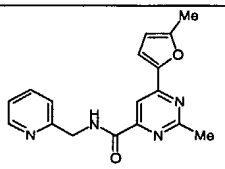
EXAMPLES

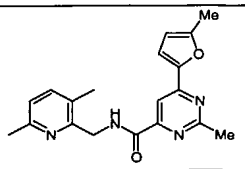
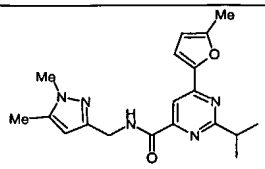
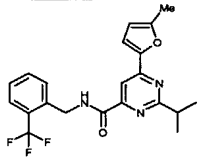
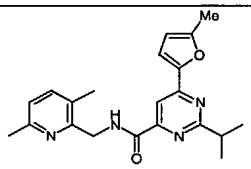
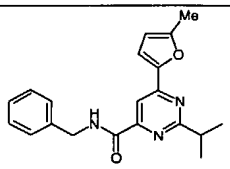
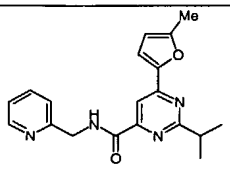
Synthetic Examples

The present invention is illustrated with reference to the following Examples, as set out in Table 1.

Table 1

Example	Structure	Compound Name
1		2-Methylamino-6-(5-methyl-2-furyl)-*N*-(2-pyridylmethyl)pyrimidine-4-carboxamide

2		2-Dimethylamino-*N*-(1,5-dimethyl-1*H*-pyrazol-3-ylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
3		2-Dimethylamino-*N*-(3,6-dimethylpyridin-2-ylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
4		*N*-Benzyl-2-dimethylamino-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
5		2-Dimethylamino-*N*-(2-pyridylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
6		2-Dimethylamino-6-(5-methyl-2-furyl)-*N*-(2-trifluoromethylbenzyl)pyrimidine-4-carboxamide
7		*N*-(1,5-Dimethyl-1*H*-pyrazol-3-ylmethyl)-2-methyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
8		2-Methyl-6-(5-methyl-2-furyl)-*N*-(2-trifluoromethylbenzyl)pyrimidine-4-carboxamide
9		*N*-Benzyl-2-methyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
10		2-Methyl-6-(5-methyl-2-furyl)-*N*-(2-pyridylmethyl)pyrimidine-4-carboxamide

11		*N*-(3,6-Dimethylpyridin-2-ylmethyl)-2-methyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
12		*N*-(1,5-Dimethyl-1*H*-pyrazol-3-ylmethyl)-2-isopropyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
13		2-Isopropyl-6-(5-methyl-2-furyl)-*N*-(2-trifluoromethylbenzyl)pyrimidine-4-carboxamide
14		*N*-(3,6-Dimethylpyridin-2-ylmethyl)-2-isopropyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
15		*N*-Benzyl-2-isopropyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
16		2-Isopropyl-6-(5-methyl-2-furyl)-*N*-(2-pyridylmethyl)pyrimidine-4-carboxamide

The general synthetic methods used for the preparation of these Examples are set out below as Methods A to E. Table 2 sets out the Method used and yield obtained for each Example, together with the analytical data.

Method A

2,4-Dichloro-6-(5-methylfuran-2-yl)pyrimidine

A mixture of 2,4,6-trichloropyrimide (5.50 g, 30 mmol), 5-methylfuran-2-boronic acid, methyl ester (4.91 g, 30 mmol), saturated aqueous $NaHCO_3$ (30 mL) and THF (30 mL) was degassed with a stream of nitrogen for 10 min, treated with palladium(0) tetrakis(triphenylphosphine) (1.73 g, 1.5 mmol), refluxed under nitrogen for 18 h, cooled, diluted with water (50 mL), extracted with DCM (3 x 50 mL) and the combined organic phase dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by

chromatography [SiO_2; hexane:EtOAc (100:0 – 90:10)] to give the *title compound* (5.08 g, 74 %) as a pale-yellow solid; NMR δ_H (400 MHz, $CDCl_3$) 2.42 (3H, s), 6.22 – 6.23 (1H, m), 7.30 – 7.31 (1H, m) and 7.47 (1H, s).

The following novel intermediates were also synthesised by Method A from the appropriate dichloropyrimidine.

4-Chloro-N,N-dimethyl-6-(5-methylfuran-2-yl)pyrimidine-2-methanamine

NMR δ_H (400 MHz, CD_3OD) 2.38 (3H, s), 3.17 (6H, s), 6.20 – 6.22 (1H, m), 6.76 (1H, s) and 7.10 – 7.11 (1H, m); M/Z 238, 240 $(M+H)^+$

4-Chloro-2-methyl-6-(5-methyl-2-furyl)pyrimidine

NMR δ_H (400 MHz, $CDCl_3$) 2.42 (3H, s), 2.70 (3H, s), 6.19 (1H, d, *J* 3.4 Hz), 7.22 (1H, d, *J* 3.4 Hz) and 7.39 (1H, s); M/Z 209, 211 $(M+H)^+$

4-Chloro-6-(5-methyl-2-furyl)-2-isopropylpyrimidine

NMR δ_H (400 MHz, $CDCl_3$) 1.28 (6H, d, *J* 6.9 Hz), 2.34 (3H, s), 3.10 (1H, sept, *J* 6.9 Hz), 6.12 (1H, d, *J* 2.3 Hz), 7.16 (1H, d, *J* 3.4 Hz) and 7.31 (1H, s); M/Z 237, 239 $(M+H)^+$

Method B

4-Chloro-6-(5-methylfuran-2-yl)pyrimidine-2-methanamine

A solution of 2,4-dichloro-6-(5-methylfuran-2-yl)pyrimidine (0.70 g, 3.07 mmol) in MeOH (5 mL) was treated with 2-M methylamine in EtOH (2 mL, 4 mmol), heated at 80 °C for 30 min, cooled, concentrated *in vacuo* and purified by chromatography [SiO_2; hexane:EtOAc (100:0 – 90:10)] to give the *title compound* (0.17 g, 22 %) as a white solid; NMR δ_H (400 MHz, CD_3OD) 2.38 (3 H, s), 2.93 (3 H, s), 6.22 – 6.23 (1 H, m), 6.83 (1 H, s) and 7.12 – 7.13 (1 H, m); M/Z 224 and 226 $(M+H)^+$

Method C

2-Methylamino-6-(5-methylfuran-2-yl)pyrimidine-4-carbonitrile

A solution of 4-chloro-6-(5-methylfuran-2-yl)pyrimidine-2-methanamine (0.17 g, 0.76 mmol), sodium cyanide (0.22 g, 4.56 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.09 g, 0.76 mmol) in 1-methyl-2-pyrrolidinone (6 mL) was heated at 80 °C for 1.5 h, cooled, poured onto an ice-water mixture. The resulting precipitate was filtered, dissolved in a

mixture of DCM (10 mL) and MeOH (10 mL), concentrated *in vacuo* and the brown solid purified by chromatography [hexane–EtOAc (0–10%) as eluent] to give the *title compound* (0.073 g, 45 %) as a white solid; NMR δ_H (400 MHz, CD_3OD) 2.40 (3H, s), 2.93 (3H, s), 6.26 – 6.27 (1H, m), 7.16 (1H, s) and 7.21 – 7.22 (1H, m); M/Z 215 $(M+H)^+$

The following novel intermediates were also synthesised by Method C from the appropriate chloropyrimidine.

2-Dimethylamino-6-(5-methylfuran-2-yl)pyrimidine-4-carbonitrile

NMR δ_H (400 MHz, CD_3OD) 2.40 (3H, s), 3.20 (6H, s), 6.25 – 6.26 (1H, m), 7.11 (1H, s) and 7.21 – 7.22 (1H, m); M/Z 229 $(M+H)^+$

2-Methyl-6-(5-methyl-2-furyl)pyrimidine-4-carbonitrile

NMR δ_H (400 MHz, $CDCl_3$) 2.44 (3H, s), 2.75 (3H, s), 6.24 (1H, d, *J* 3.4 Hz), 7.30 (1H, d, *J* 3.4 Hz) and 7.65 (1H, s); M/Z 200 $(M+H)^+$

2-Isopropyl-6-(5-methyl-2-furyl)pyrimidine-4-carbonitrile

NMR δ_H (400 MHz, $CDCl_3$) 1.28 (6H, d, *J* 6.9 Hz), 2.37 (3H, s), 3.15 (1H, sept, *J* 6.9 Hz), 6.16 (1H, d, *J* 2.6 Hz), 7.24 (1H, d, *J* 3.3 Hz) and 7.57 (1H, s); M/Z 228 $(M+H)^+$

Method D

2-Methylamino-6-(5-methylfuran-2-yl)pyrimidine-4-carboxylic acid

A solution of 2-methylamino-6-(5-methylfuran-2-yl)pyrimidine-4-carbonitrile (0.073 g, 0.34 mmol) in water (4 mL) and concentrated H_2SO_4 (4 mL) was refluxed for 4 h, cooled and poured onto ice. The resulting non-solid mixture was loaded directly onto an acidic ion-exchange column (Isolute® Flash SCX-2) and eluted with DCM - MeOH, followed by 1-M ammonia in MeOH to give the title compound (0.08 g, quantitative) as a pale-brown solid; NMR δ_H (400 MHz, CD_3OD) 2.39 (3H, s), 2.99 (3H, s), 6.21 – 6.22 (1H, m), 7.11 – 7.12 (1H, m) and 7.33 (1H, s); M/Z 234 $(M+H)^+$

The following novel intermediates were also synthesised by Method D from the appropriate pyrimidine-4-carbonitrile.

2-Dimethylamino-6-(5-methylfuran-2-yl)pyrimidine-4-carboxylic acid

NMR δ_H (400 MHz, CD_3OD) 2.38 (3H, s), 3.23 (6H, s), 6.19 – 6.20 (1H, m), 7.08 – 7.09 (1H, m) and 7.31 (1H, s); M/Z 248 $(M+H)^+$

2-Methyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxylic acid

NMR δ_H (400 MHz, d_6-DMSO) 2.68 (3H, s), 3.18 (3H, s), 6.42 (1H, d, *J* 3.3 Hz), 7.44 (1H, d, *J* 3.3 Hz) and 7.94 (1H, s)

2-Isopropyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxylic acid

NMR δ_H (400 MHz, $CDCl_3$) 1.39 (6H, d, *J* 6.9 Hz), 2.45 (3H, s), 3.28 (1H, sept, *J* 6.9 Hz), 6.23 (1H, d, *J* 3.3 Hz), 7.33 (1H, d, *J* 3.4 Hz) and 8.14 (1H, s); M/Z 247 $(M+H)^+$

Method E

2-Methylamino-6-(5-methylfuran-2-yl)-N-(2-pyridylmethyl)pyrimidine-4-carboxamide (Example 1)

A mixture of 2-methylamino-6-(5-methylfuran-2-yl)pyrimidine-4-carboxylic acid (0.080 g, 0.34 mmol), pyridine-2-methanamine (0.074 g, 0.68 mmol), polymer supported carbodiimide (0.86 g, 1.04 mmol), 1-hydroxybenzotriazole (0.07 g, 0.52 mmol) and *N,N'*-diisopropylethylamine (0.09 ml, 0.52 mmol) in dimethyl formamide (5 mL) was stirred at room temperature for 16 h, filtered through Celite, and the filtrate was partitioned between water (25 mL) and EtOAc (25 mL). The aqueous phase was extracted with EtOAc (2 x 25 mL), the combined organic phase was dried ($MgSO_4$) concentrated *in vacuo* and the resulting syrup purified by chromatography [SiO_2, hexane:EtOAc (100:0 – 0:100)]. The resulting yellow gum, was purified by preparative LC-MS under a gradient elution (0 min, 5% solvent B; 0.75 min, 30% B; 6.0 min, 75% B; 7.5 min, 95% B; 9.5 min, 95% B; 10.0 min, 5% B) to give the *title compound* (0.01 g, 9 %) as an off-white solid; NMR δ_H (400 MHz, CD_3OD) 2.40 (3H, s), 3.02 (3H, s), 4.71 (2H, s), 6.23 – 6.24 (1H, m), 7.16 (1H, d, *J* 3.5 Hz), 7.32 (1H, dd, *J* 7.5, 5.5 Hz), 7.42 (1H, d, *J* 7.5 Hz), 7.46 (1H, s), 7.78 – 7.83 (1H, m) and 8.50 (1H, d, *J* 4.5 Hz); M/Z 324 $(M+H)^+$.

General method for preparative LC-MS

Preparative LC-MS was performed at ambient temperature on a Waters FractionLynx MS autopurification system using a Luna 5 μm, C18(2), 100 mm x 21.2 mm i.d. column from Phenomenex. Solvent A: water + 0.08% v/v formic acid, solvent B: 95% methanol-water + 0.08% v/v formic acid, flow rate: 20 ml min^{-1}. The instrument incorporated a photo diode array detector (210–400 nm) and a MicroMass ZQ mass spectrometer. The ionisation

method was positive ion electrospray and the molecular weight scan range was 150–1000. Collection was triggered by detection of the selected mass ion.

Table 2

Example	Method	Yield (%)	Physical Data
1	E	9	NMR δ_H (400 MHz, CD_3OD) 2.40 (3H, s), 3.02 (3H, s), 4.71 (2H, s), 6.23 – 6.24 (1H, m), 7.16 (1H, d, *J* 3.5 Hz), 7.32 (1H, dd, *J* 7.5, 5.5 Hz), 7.42 (1H, d, *J* 7.5 Hz), 7.46 (1H, s), 7.78 – 7.83 (1H, m) and 8.50 (1H, d, *J* 4.5 Hz); M/Z 324 $(M+H)^+$
2	E	42	NMR δ_H (400 MHz, CD_3OD) 2.25 (3H, s), 2.39 (3H, s), 3.23 (6H, s), 3.71 (3H, s), 4.49 (2H, s), 6.01 (1H, s), 6.22 – 6.23 (1H, m), 7.14 – 7.15 (1H, m) and 7.41 (1H, s); M/Z 355 $(M+H)^+$
3	E	15	NMR δ_H (400 MHz, CD_3OD) 2.33 (3H, s), 2.40 (3H, s), 2.50 (3H, s), 3.30 (6H, s), 4.60 (2H, s), 6.23 – 6.24 (1H, m), 7.09 (1H, d, *J* 7.5 Hz), 7.15 (1H, d, *J* 3.5 Hz), 7.45 (1H, s) and 7.48 (1H, d, *J* 7.5 Hz); M/Z 366 $(M+H)^+$
4	E	41	NMR δ_H (400 MHz, CD_3OD) 2.40 (3H, s), 3.24 (6H, s), 4.60 (2H, s), 6.22 – 6.23 (1H, m), 7.15 (1H, d, *J* 3.5 Hz), 7.22 – 7.26 (1H, m), 7.30 – 7.36 (4H, m) and 7.44 (1H, s); M/Z 337 $(M+H)^+$
5	E	26	NMR δ_H (400 MHz, CD_3OD) 2.39 (3H, s), 3.26 (6H, s), 4.71 (2H, s), 6.22 – 6.23 (1H, m), 7.14 (1H, d, *J* 3.5 Hz), 7.29 – 7.32 (1H, m), 7.42 (1H, s), 7.80 (1H, dt, *J* 7.5, 2.0 Hz) and 8.49 – 8.51 (1H, m); M/Z 338 $(M+H)^+$
6	E	17	NMR δ_H (400 MHz, CD_3OD) 2.40 (3H, s), 3.25 (6H, s), 6.23 – 6.24 (1H, m), 7.16 (1H, d, *J* 3.5 Hz), 7.43 – 7.46 (2H, m), 7.54 – 7.61 (2H, m) and 7.71 – 7.72 (1H, m); M/Z 405 $(M+H)^+$
7	E	38	NMR δ_H (400 MHz, $CDCl_3$) 2.18 (3H, s), 2.38 (3H, s), 2.69 (3H, s), 3.71 (3H, s), 4.54 (2H, d, *J* 5.9 Hz), 5.98 (1H, s), 6.13 (1H, d, *J* 3.4 Hz), 7.16 (1H, d, *J* 3.3 Hz), 8.07 (1H, s) and 8.36 (1H, br s); M/Z 326 $(M+H)^+$
8	E	47	NMR δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s), 2.67 (3H, s), 4.80 (2H, d, *J* 6.4 Hz), 6.14 (1H, d, *J* 3.4 Hz), 7.18 (1H, d, *J* 3.4 Hz), 7.34 (1H, t, *J* 7.7 Hz), 7.48 (1H, t, *J* 7.3 Hz), 7.56 (1H, d, *J* 7.7 Hz), 7.64 (1H, d, *J* 7.2 Hz), 8.08 (1H, s) and 8.38 (1H, br s); M/Z 376 $(M+H)^+$

9	E	35	NMR δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s), 2.65 (3H, s), 4.62 (2H, d, *J* 6.2 Hz), 6.13 (1H, d, *J* 3.4 Hz), 7.31 - 7.17 (6H, m), 8.10 (1H, s) and 8.30 (1H, br s); M/Z 308 $(M+H)^+$
10	E	35	NMR δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s), 2.70 (3H, s), 4.75 (2H, d, *J* 5.8 Hz), 6.14 (1H, d, *J* 3.4 Hz), 7.18 - 7.16 (2H, m), 7.31 (1H, d, *J* 7.8 Hz), 7.64 (1H, td, *J* 7.7, 1.8 Hz), 8.08 (1H, s), 8.57 - 8.55 (1H, m) and 8.88 (1H, br s); M/Z 309 $(M+H)^+$
11	E	40	NMR δ_H (400 MHz, $CDCl_3$) 2.31 (3H, s), 2.44 (3H, s), 2.59 (3H, s), 2.81 (3H, s), 4.68 (2H, br s), 6.20 (1H, s), 7.03 (1H, d, *J* 7.8 Hz), 7.26 - 7.23 (1H, m), 7.39 (1H, d, *J* 7.4 Hz), 8.16 (1H, s) and 9.48 (1H, br s); M/Z 337 $(M+H)^+$
12	E	36	NMR δ_H (400 MHz, $CDCl_3$) 1.35 (6H, d, *J* 6.9 Hz), 2.25 (3H, s), 2.42 (3H, s), 3.21 (1H, sept, *J* 6.9 Hz), 3.84 (3H, s), 4.61 (2H, d, *J* 5.9 Hz), 6.05 (1H, s), 6.18 (1H, d, *J* 3.3 Hz), 7.23 (1H, d, *J* 3.4 Hz), 8.14 (1H, s) and 8.47 (1H, br s); M/Z 354 $(M+H)^+$
13	E	44	NMR δ_H (400 MHz, $CDCl_3$) 1.28 (6H, d, *J* 6.9 Hz), 2.36 (3H, s), 3.16 (1H, sept, *J* 6.9 Hz), 4.80 (2H, d, *J* 6.5 Hz), 6.12 (1H, d, *J* 3.3 Hz), 7.19 (1H, d, *J* 3.5 Hz), 7.34 (1H, t, *J* 7.6 Hz), 7.48 (1H, t, *J* 7.5 Hz), 7.58 (1H, d, *J* 7.7 Hz), 7.63 (1H, d, *J* 7.6 Hz), 8.07 (1H, s) and 8.46 (1H, br s); M/Z 404 $(M+H)^+$
14	E	38	NMR δ_H (400 MHz, $CDCl_3$) 1.37 (6H, d, *J* 6.9 Hz), 2.23 (3H, s), 2.37 (3H, s), 2.52 (3H, s), 3.24 (1H, sept, *J* 6.9 Hz), 4.60 (2H, d, *J* 4.2 Hz), 6.12 (1H, d, *J* 2.6 Hz), 6.96 (1H, d, *J* 7.6 Hz), 7.18 (1H, d, *J* 3.5 Hz), 7.33 (1H, d, *J* 7.6 Hz), 8.09 (1H, s) and 9.94 (1H, br s); M/Z 365 $(M+H)^+$
15	E	32	NMR δ_H (400 MHz, $CDCl_3$) 1.27 (6H, d, *J* 6.9 Hz), 2.36 (3H, s), 3.15 (1H, sept, *J* 6.9 Hz), 4.63 (2H, d, *J* 6.2 Hz), 6.12 (1H, d, *J* 2.7 Hz), 7.19 (1H, d, *J* 2.8 Hz), 7.32 - 7.24 (5H, m), 8.10 (1H, s) and 8.35 (1H, br s); M/Z 336 $(M+H)^+$
16	E	32	NMR δ_H (400 MHz, $CDCl_3$) 1.40 (6H, d, *J* 6.9 Hz), 2.44 (3H, s), 3.27 (1H, sept, *J* 6.9 Hz), 4.84 (2H, d, *J* 5.8 Hz), 6.21 (1H, d, *J* 3.3 Hz), 7.26 - 7.24 (2H, m), 7.40 (1H, d, *J* 7.8 Hz), 7.72 (1H, td, *J* 7.7, 1.6 Hz), 8.16 (1H, s), 8.63 (1H, d, *J* 4.3 Hz) and 9.05 (1H, br s); M/Z 337 $(M+H)^+$

Adenosine Receptor Binding

Binding Affinities at hA_{2A} Receptors

The compounds were examined in an assay measuring *in vitro* binding to human adenosine A_{2A} receptors by determining the displacement of the adenosine A_{2A} receptor selective radioligand [^{3}H]-CGS 21680 using standard techniques.

Synthetic examples 1 – 16 detailed in Table 1 have a K_i of <5 μM in this assay demonstrating binding affinity for the human adenosine A_{2A} receptor. By way of illustration only, example 1 has a K_i of <100 nM in this assay.

Evaluation of potential anti-Parkinsonian activity *in vivo*

A model of Parkinson's Disease for assessment of the compounds of the invention is as follows

Haloperidol-induced hypolocomotion model

It has previously been demonstrated that adenosine antagonists, such as theophylline, can reverse the behavioural depressant effects of dopamine antagonists, such as haloperidol, in rodents (Mandhane S.N. *et al.,* Adenosine A_2 receptors modulate haloperidol-induced catalepsy in rats. *Eur. J. Pharmacol.* 1997, **328**, 135 - 141). This approach is also considered a valid method for screening drugs with potential antiparkinsonian effects. Thus, the ability of novel adenosine antagonists to block haloperidol-induced deficits in locomotor activity in mice can be used to assess both *in vivo* and potential antiparkinsonian efficacy.

Method

Female TO mice (25-30g) obtained from Harlan, UK, are used for all experiments. Animals are housed in groups of 8 [cage size – 40 (width) x 40 (length) x 20 (height)cm] under 12 h light/dark cycle (lights on 08:00hr), in a temperature (20 ± 2°C) and humidity (55 ± 15%) controlled environment. Animals have free access to food and water, and are allowed at least 3 days to acclimatize after delivery before experimental use.

Drugs

Liquid injectable haloperidol (1 ml Serenance ampoules from Baker Norton, Harlow, Essex, each containing haloperidol BP 5 mg) are diluted to a final concentration of 0.02 mg/ml using saline. Test compounds are typically prepared as aqueous suspensions in 1 % methyl cellulose. All compounds are administered orally in a volume of 10 ml/kg.

Procedure

1.5 h before testing, mice are administered 0.2 mg/kg haloperidol, a dose that reduces baseline locomotor activity by at least 50 %. Test substances are typically administered 5 - 60 min. prior to testing. The animals are then placed individually into clean, clear polycarbonate cages [20 (width) x 40 (length) x 20 (height) cm, with a flat perforated, Perspex lid]. Horizontal locomotor activity is determined by placing the cages within a frame containing a 4 x 7 array of photocells linked to a computer, which tabulates beam breaks. Mice are left undisturbed to explore for up to 1 h, and the number of beams breaks made during this period serves as a record of locomotor activity which is compared with data for control animals for statistically significant differences.

6-OHDA Model

An alternative model of Parkinson's Disease for assessment of the compounds of the invention is as follows

Parkinson's disease is a progressive neurodegenerative disorder characterised by symptoms of muscle rigidity, tremor, paucity of movement (hypokinesia), and postural instability. It has been established for some time that the primary deficit in PD is a loss of dopaminergic neurones in the substantia nigra which project to the striatum, and indeed a substantial proportion of striatal dopamine is lost (ca 80-85%) before symptoms are observed. The loss of striatal dopamine results in abnormal activity of the basal ganglia, a series of nuclei which regulate smooth and well co-ordinated movement (Blandini F. *et al.*, Glutamate and Parkinson's Disease. *Mol. Neurobiol.* 1996, **12**, 73 - 94). The neurochemical deficits seen in Parkinson's disease can be reproduced by local injection of the dopaminergic neurotoxin 6-hydroxydopamine into brain regions containing either the cell bodies or axonal fibres of the nigrostriatal neurones.

By unilaterally lesioning the nigrostriatal pathway on only one-side of the brain, a behavioural asymmetry in movement inhibition is observed. Although unilaterally-lesioned

animals are still mobile and capable of self maintenance, the remaining dopamine-sensitive neurones on the lesioned side become supersensitive to stimulation. This is demonstrated by the observation that following systemic administration of dopamine agonists, such as apomorphine, animals show a pronounced rotation in a direction contralateral to the side of lesioning. The ability of compounds to induce contralateral rotations in 6-OHDA lesioned rats has proven to be a sensitive model to predict drug efficacy in the treatment of Parkinson's Disease.

Animals

Male Sprague-Dawley rats, obtained from Charles River, are used for all experiments. Animals are housed in groups of 5 under 12hr light/dark cycle (lights on 08:00hr), in a temperature (20 ± 2°C) and humidity (55 ± 15%) controlled environment. Animals have free access to food and water, and are allowed at least 7 days to acclimatize after delivery before experimental use.

Drugs

Ascorbic acid, desipramine, 6-OHDA and apomorphine (Sigma-Aldrich, Poole, UK). 6-OHDA is freshly prepared as a solution in 0.2% ascorbate at a concentration of 4 mg/mL prior to surgery. Desipramine is dissolved in warm saline, and administered in a volume of 1 ml/kg. Apomorphine is dissolved in 0.02% ascorbate and administered in a volume of 2 mL/kg. Test compounds are suspended in 1 % methyl cellulose and injected in a volume of 2 mL/kg.

Surgery

15 minutes prior to surgery, animals are given an intraperitoneal injection of the noradrenergic uptake inhibitor desipramine (25 mg/kg) to prevent damage to non-dopamine neurones. Animals are then placed in an anaesthetic chamber and anaesthetised using a mixture of oxygen and isoflurane. Once unconscious, the animals are transferred to a stereotaxic frame, where anaesthesia is maintained through a mask. The top of the animal's head is shaved and sterilised using an iodine solution. Once dry, a 2 cm long incision is made along the midline of the scalp and the skin retracted and clipped back to expose the skull. A small hole is then drilled through the skill above the injection site. In order to lesion the nigrostriatal pathway, the injection cannula is slowly lowered to position above the right medial forebrain bundle at –3.2 mm anterior posterior, -1.5 mm medial lateral from bregma, and to a depth of 7.2 mm below the duramater. 2 minutes after lowing the cannula, 2 μL of 6-OHDA solution is infused at a rate of 0.5

μL/min over 4 minutes, yielding a final dose of 8 μg. The cannula is then left in place for a further 5 minutes to facilitate diffusion before being slowly withdrawn. The skin is then sutured shut using Ethicon W501 Mersilk, and the animal removed from the strereotaxic frame and returned to its homecage. The rats are allowed 2 weeks to recover from surgery before behavioural testing.

Apparatus

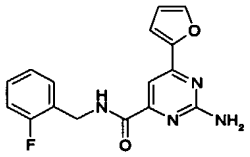
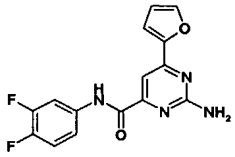
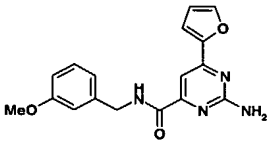
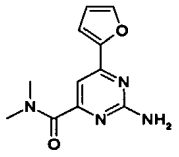
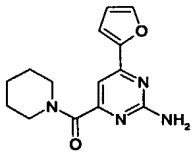
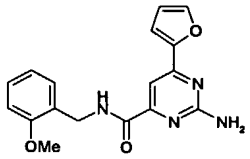
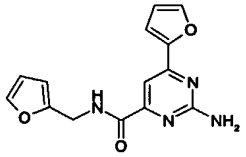
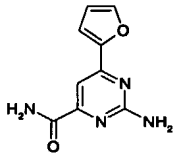
Rotational behaviour is measured using an eight station rotameter system provided by Med Associates, San Diego, USA. Each station is comprised of a stainless steel bowl (45 cm diameter x 15 cm high) enclosed in a transparent Plexiglas cover running around the edge of the bowl, and extending to a height of 29 cm. To assess rotation, rats are placed in cloth jacket attached to a spring tether connected to optical rotameter positioned above the bowl, which assesses movement to the left or right either as partial (45º) or full (360º) rotations. All eight stations are interfaced to a computer that tabulated data.

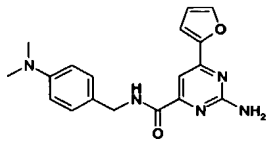
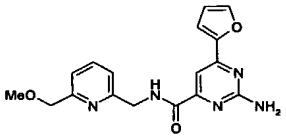
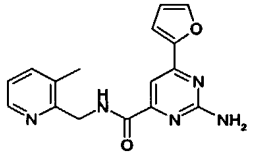
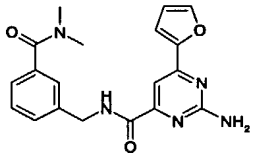
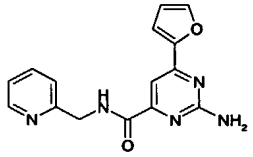
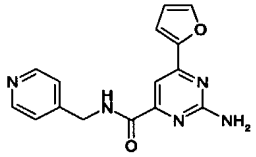
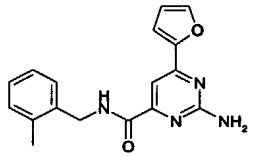
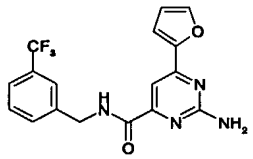
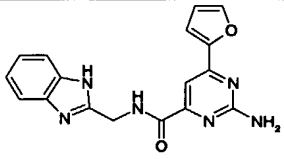
Procedure

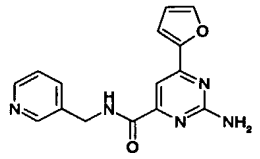
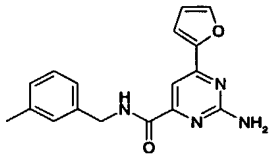
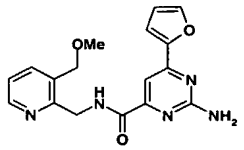
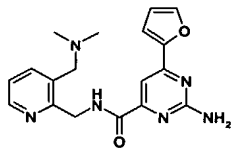
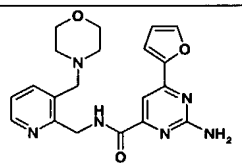
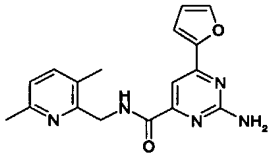
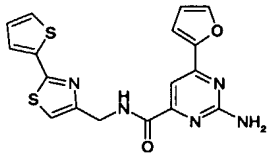
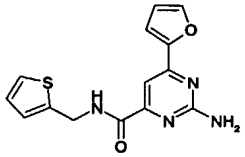
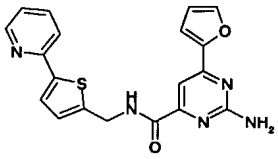
To reduce stress during drug testing, rats are initially habituated to the apparatus for 15 minutes on four consecutive days. On the test day, rats are given an intraperitoneal injection of test compound 30 minutes prior to testing. Immediately prior to testing, animals are given a subcutaneous injection of a subthreshold dose of apomorphine, then placed in the harness and the number of rotations recorded for one hour. The total number of full contralateral rotations during the hour test period serves as an index of antiparkinsonian drug efficacy.

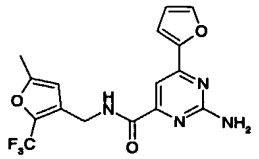
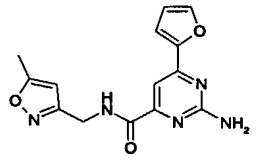
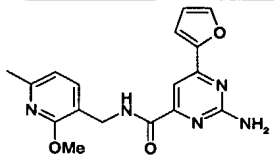
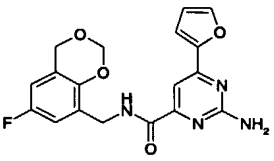
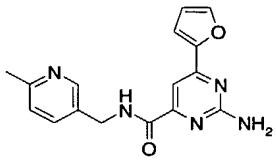
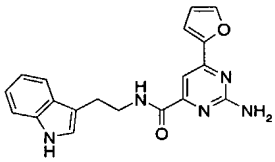
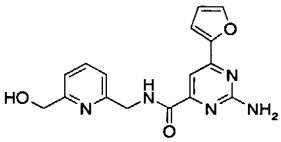
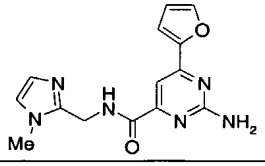
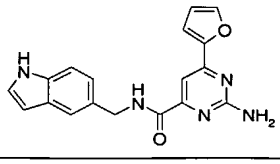
Table 3 lists compounds that are closely analogous in structure to the compounds of the present invention and which are effective as A2A antagonists. Although the Table 3 compounds are outside the scope of the present invention, their close structural similarity to the compounds with which this invention is concerned suggests that the equivalent substituent groups R_2 to R_5 are suitable for use in the present compounds.

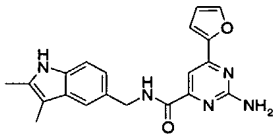
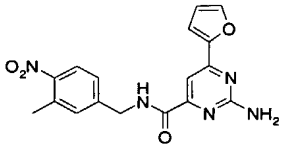
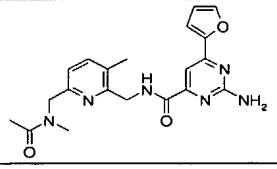
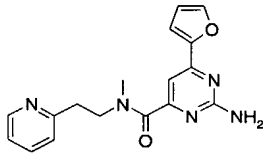
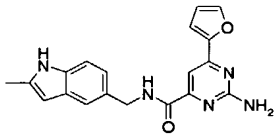
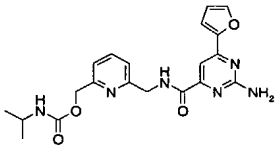
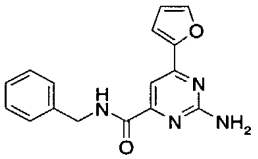
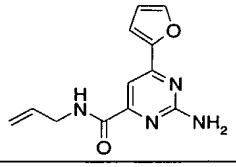
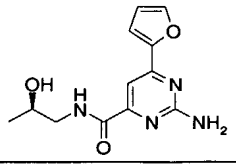
Table 3

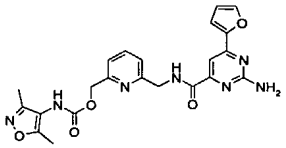
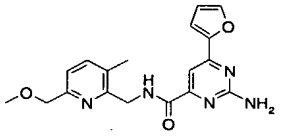
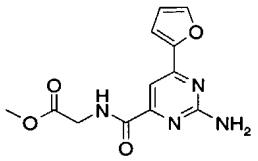
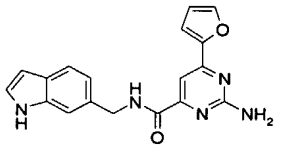
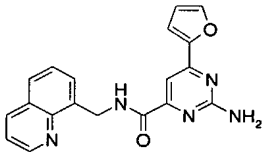
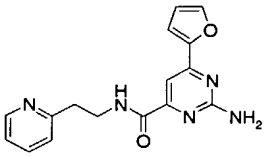
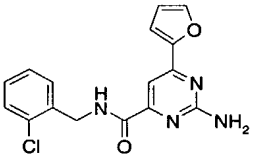
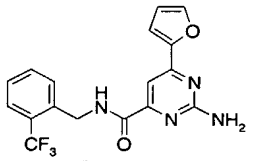
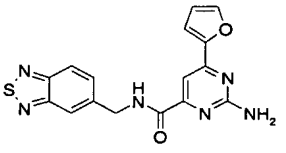
Example	Structure	Compound Name
17		2-Amino-*N*-(2-fluorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
18		2-Amino-*N*-(3,4-difluorophenyl)-6-(2-furyl)pyrimidine-4-carboxamide
19		2-Amino-6-(2-furyl)-*N*-(3-methoxybenzyl)pyrimidine-4-carboxamide
20		2-Amino-6-(2-furyl)-*N*,*N*-dimethylpyrimidine-4-carboxamide
21		1-(2-Amino-6-(2-furyl)pyrimidin-4-ylcarbonyl)piperidine
22		2-Amino-6-(2-furyl)-*N*-(2-methoxybenzyl)pyrimidine-4-carboxamide
23		2-Amino-6-(2-furyl)-*N*-(2-furylmethyl)pyrimidine-4-carboxamide
24		2-Amino-6-(2-furyl)pyrimidine-4-carboxamide

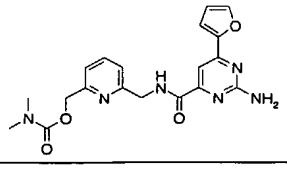
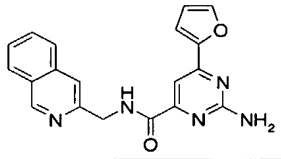
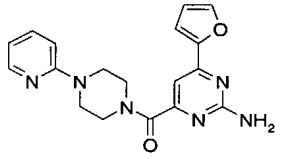
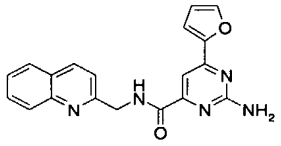
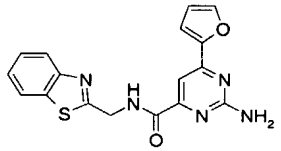
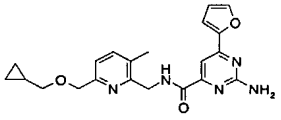
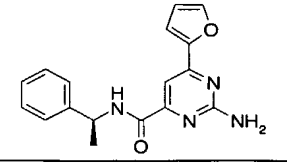
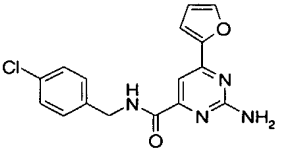
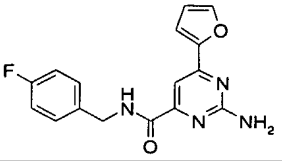
25		2-Amino-6-(2-furyl)-*N*-(4-dimethylaminobenzyl)pyrimidine-4-carboxamide
26		2-Amino-6-(2-furyl)-*N*-(6-methoxymethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
27		2-Amino-6-(2-furyl)-*N*-(3-methylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
28		2-Amino-6-(2-furyl)-*N*-(3-(dimethylaminocarbonyl)benzyl)pyrimidine-4-carboxamide
29		2-Amino-6-(2-furyl)-*N*-(2-pyridylmethyl)pyrimidine-4-carboxamide
30		2-Amino-6-(2-furyl)-*N*-(4-pyridylmethyl)pyrimidine-4-carboxamide
31		2-Amino-6-(2-furyl)-*N*-(2-methylbenzyl)pyrimidine-4-carboxamide
32		2-Amino-*N*-(3-trifluoromethylbenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
33		2-Amino-*N*-(1*H*-benzimidazol-2-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide

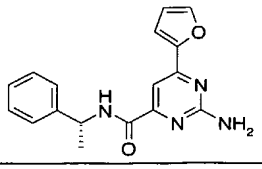
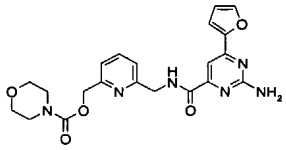
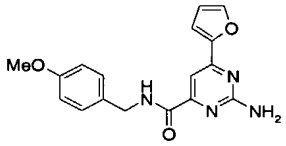
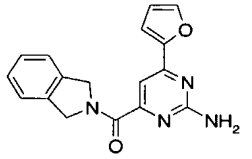
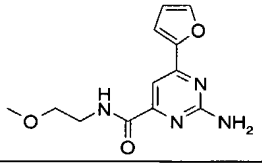
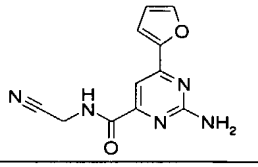
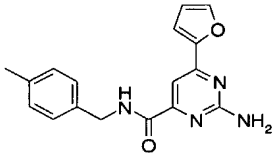
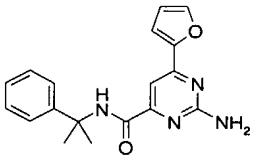
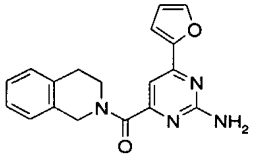
34		2-Amino-6-(2-furyl)-*N*-(3-pyridylmethyl)pyrimidine-4-carboxamide
35		2-Amino-6-(2-furyl)-*N*-(3-methylbenzyl)pyrimidine-4-carboxamide
36		2-Amino-6-(2-furyl)-*N*-(3-methoxymethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
37		2-Amino-6-(2-furyl)-*N*-(3-dimethylaminomethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
38		2-Amino-6-(2-furyl)-*N*-(3-(4-morpholinylmethyl)pyridin-2-ylmethyl)pyrimidine-4-carboxamide
39		2-Amino-6-(2-furyl)-*N*-(3,6-dimethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
40		2-Amino-6-(2-furyl)-*N*-(2-(2-thienyl)thiazol-4-ylmethyl)pyrimidine-4-carboxamide
41		2-Amino-6-(2-furyl)-*N*-(2-thienylmethyl)pyrimidine-4-carboxamide
42		2-Amino-6-(2-furyl)-*N*-(5-(2-pyridyl)-2-thienylmethyl)pyrimidine-4-carboxamide

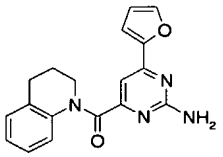
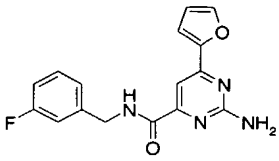
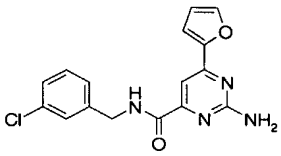
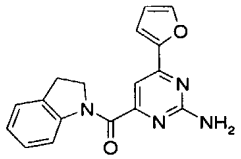
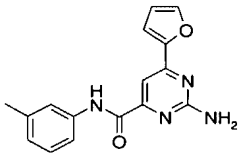
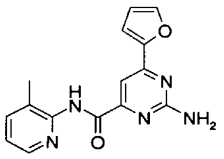
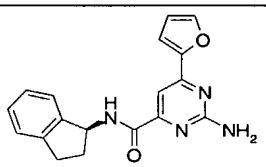
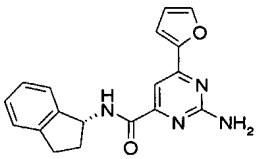
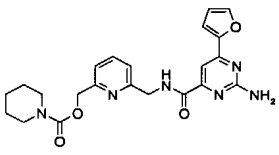
43		2-Amino-6-(2-furyl)-*N*-(5-methyl-2-trifluoromethylfuran-3-ylmethyl)pyrimidine-4-carboxamide
44		2-Amino-6-(2-furyl)-*N*-(5-methylisoxazol-3-ylmethyl)pyrimidine-4-carboxamide
45		2-Amino-6-(2-furyl)-*N*-(2-methoxy-6-methylpyridin-3-ylmethyl)pyrimidine-4-carboxamide
46		2-Amino-*N*-(6-fluoro[1,3]benzodioxin-8-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide
47		2-Amino-6-(2-furyl)-*N*-(6-methylpyridin-3-ylmethyl)pyrimidine-4-carboxamide
48		2-Amino-6-(2-furyl)-*N*-(3-indolylmethyl)pyrimidine-4-carboxamide
49		2-Amino-6-(2-furyl)-*N*-(6-hydroxymethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
50		2-Amino-6-(2-furyl)-*N*-(1-methyl-1*H*-imidazol-2-ylmethyl)pyrimidine-4-carboxamide
51		2-Amino-6-(2-furyl)-*N*-(5-indolylmethyl)pyrimidine-4-carboxamide

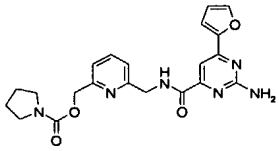
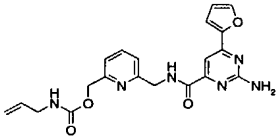
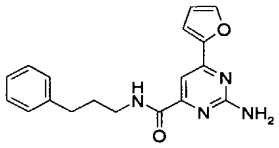
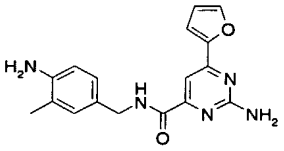
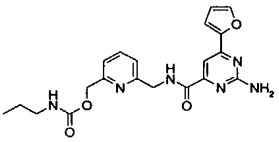
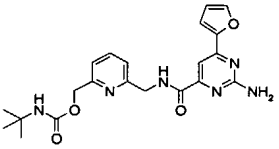
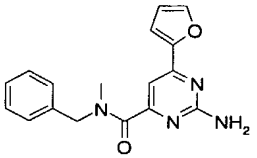
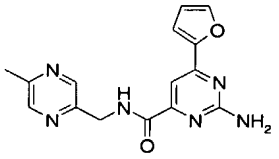
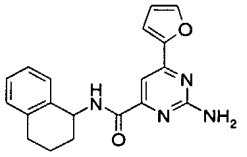
52		2-Amino-*N*-(2,3-dimethylindol-5-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide
53		2-Amino-6-(2-furyl)-*N*-(3-methyl-4-nitrobenzyl)pyrimidine-4-carboxamide
54		*N*-(6-(*N*-Acetyl-*N*-methylaminomethyl)-3-methylpyridin-2-ylmethyl)-2-amino-6-(2-furyl)pyrimidine-4-carboxamide
55		2-Amino-6-(2-furyl)-*N*-methyl-*N*-(2-(2-pyridyl)ethyl)pyrimidine-4-carboxamide
56		2-Amino-6-(2-furyl)-*N*-(2-methylindol-5-ylmethyl)pyrimidine-4-carboxamide
57		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl isopropylcarbamate
58		2-Amino-*N*-benzyl-6-(2-furyl)pyrimidine-4-carboxamide
59		*N*-Allyl-2-amino-6-(2-furyl)pyrimidine-4-carboxamide
60		(R)-2-Amino-6-(2-furyl)-*N*-(2-hydroxypropyl)pyrimidine-4-carboxamide

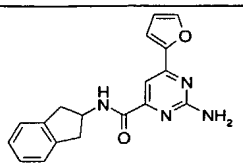
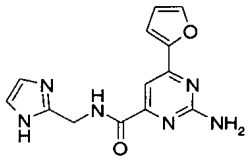
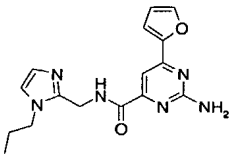
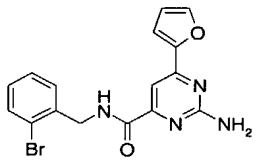
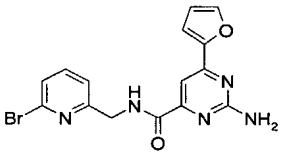
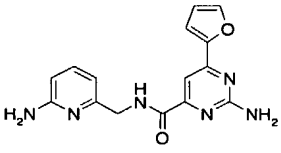
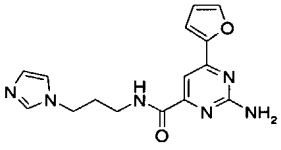
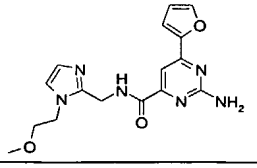
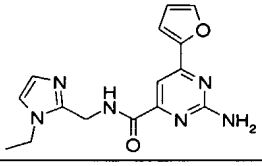
61		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl 3,5-dimethyloxazol-4-ylcarbamate
62		2-Amino-6-(2-furyl)-*N*-(6-methoxymethyl-3-methylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
63		Methyl 2-amino-6-(2-furyl)pyrimidine-4-carboxamidoacetate
64		2-Amino-6-(2-furyl)-*N*-(6-indolylmethyl)pyrimidine-4-carboxamide
65		2-Amino-6-(2-furyl)-*N*-(quinolin-8-ylmethyl)pyrimidine-4-carboxamide
66		2-Amino-6-(2-furyl)-*N*-(2-(pyridin-2-yl)ethyl)pyrimidine-4-carboxamide
67		2-Amino-*N*-(2-chlorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
68		2-Amino-6-(2-furyl)-*N*-(2-trifluoromethylbenzyl)pyrimidine-4-carboxamide
69		2-Amino-*N*-([2,1,3]benzothiadiazol-5-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide

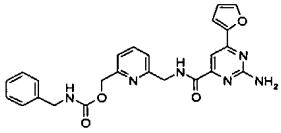
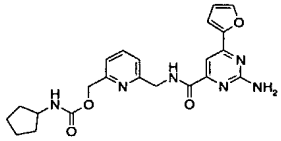
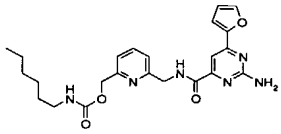
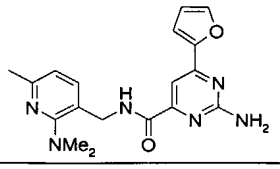
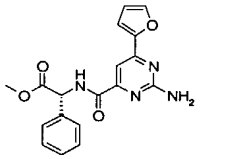
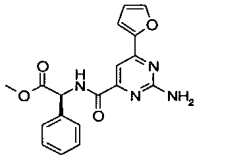
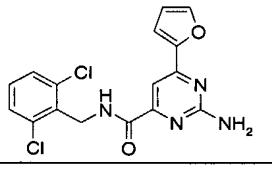
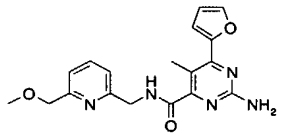
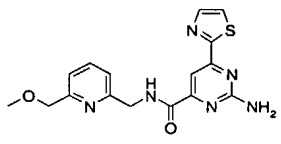
70		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl dimethylcarbamate
71		2-Amino-6-(2-furyl)-*N*-(isoquinolin-3-ylmethyl)pyrimidine-4-carboxamide
72		1-(2-Amino-6-(2-furyl)pyrimidin-4-ylcarbonyl)-4-(2-pyridyl)piperazine
73		2-Amino-6-(2-furyl)-*N*-(quinolin-2-ylmethyl)pyrimidine-4-carboxamide
74		2-Amino-*N*-(benzothiazol-2-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide
75		2-Amino-*N*-(6-cyclopropylmethoxymethyl-3-methylpyridin-2-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide
76		(S)-2-Amino-6-(2-furyl)-*N*-(1-phenylethyl)pyrimidine-4-carboxamide
77		2-Amino-*N*-(4-chlorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
78		2-Amino-*N*-(4-fluorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide

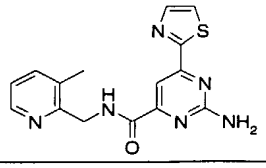
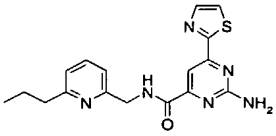
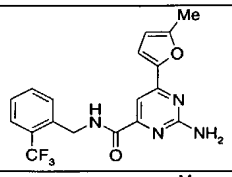
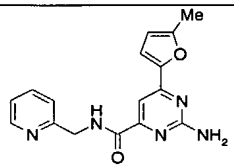
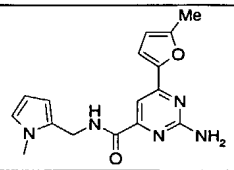
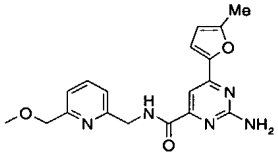
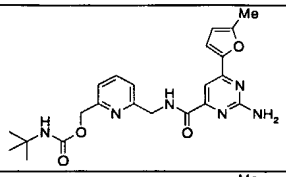
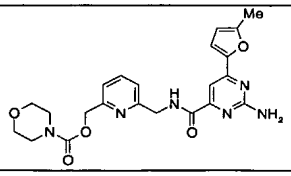
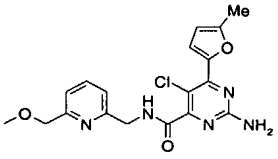
79		(R)-2-Amino-6-(2-furyl)-*N*-(1-phenylethyl)pyrimidine-4-carboxamide
80		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl morpholine-1-carboxylate
81		2-Amino-6-(2-furyl)-*N*-(4-methoxybenzyl)pyrimidine-4-carboxamide
82		2-(2-Amino-6-(2-furyl)pyrimidin-4-ylcarbonyl)-2,3-dihydro-1*H*-isoindole
83		2-Amino-6-(2-furyl)-*N*-(2-methoxyethyl)pyrimidine-4-carboxamide
84		2-Amino-*N*-(cyanomethyl)-6-(2-furyl)pyrimidine-4-carboxamide
85		2-Amino-6-(2-furyl)-*N*-(4-methylbenzyl)pyrimidine-4-carboxamide
86		2-Amino-6-(2-furyl)-*N*-(1-phenylprop-1-yl)pyrimidine-4-carboxamide
87		2-(2-Amino-6-(2-furyl)pyrimidin-4-ylcarbonyl)-1,2,3,4-tetrahydroisoquinoline

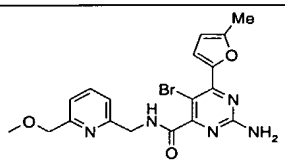
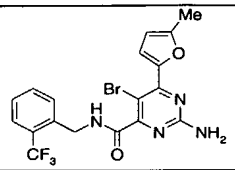
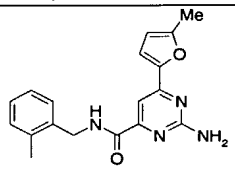
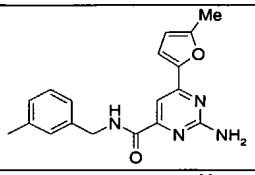
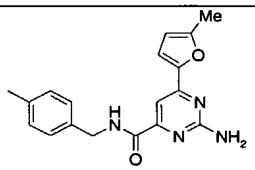
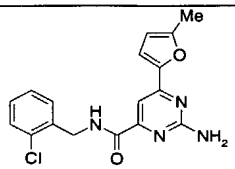
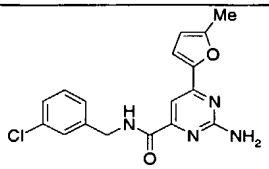
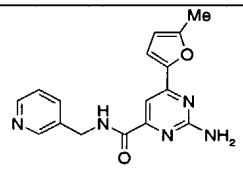
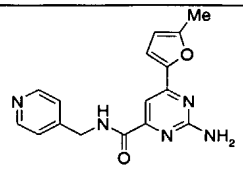
88		1-(2-Amino-6-(2-furyl)pyrimidin-4-ylcarbonyl)-1,2,3,4-tetrahydroquinoline
89		2-Amino-*N*-(3-fluorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
90		2-Amino-*N*-(3-chlorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
91		1-(2-Amino-6-(2-furyl)pyrimidin-4-ylcarbonyl)-2,3-dihydroindole
92		2-Amino-6-(2-furyl)-*N*-(3-methylphenyl)pyrimidine-4-carboxamide
93		2-Amino-6-(2-furyl)-*N*-(3-methylpyridin-2-yl)pyrimidine-4-carboxamide
94		(R)-2-Amino-6-(2-furyl)-*N*-(1-indanyl)pyrimidine-4-carboxamide
95		(S)-2-Amino-6-(2-furyl)-*N*-(1-indanyl)pyrimidine-4-carboxamide
96		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl piperidine-1-carboxylate

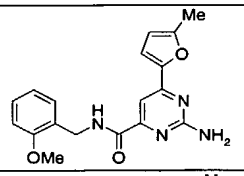
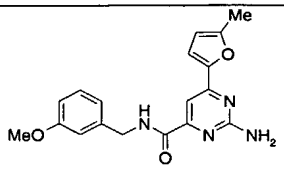
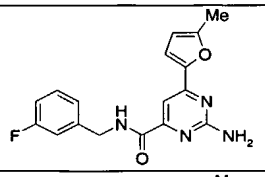
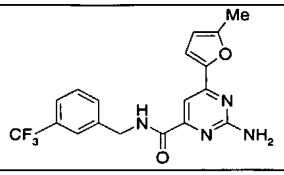
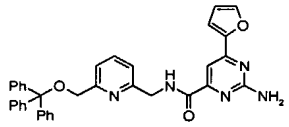
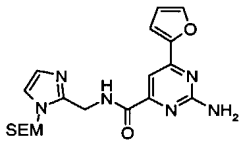
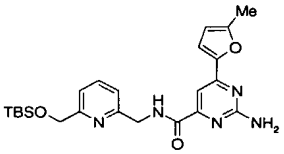
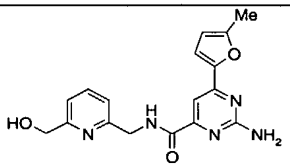
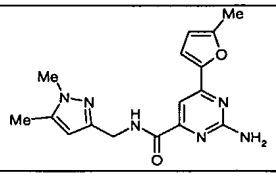
97		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl pyrrolidine-1-carboxylate
98		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl allylcarbamate
99		2-Amino-6-(2-furyl)-*N*-(3-phenylpropyl)pyrimidine-4-carboxamide
100		2-Amino-*N*-(4-amino-3-methylbenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
101		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl *n*-propylcarbamate
102		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl *tert*-butylcarbamate
103		2-Amino-*N*-benzyl-6-(2-furyl)-*N*-methylpyrimidine-4-carboxamide
104		2-Amino-6-(2-furyl)-*N*-(5-methylpyrazin-2-ylmethyl)pyrimidine-4-carboxamide
105		(R,S)-2-Amino-6-(2-furyl)-*N*-(1,2,3,4-tetrahydro-1-naphthyl)pyrimidine-4-carboxamide

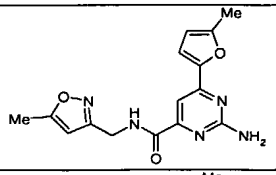
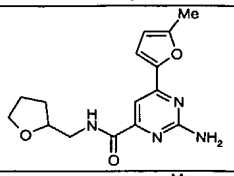
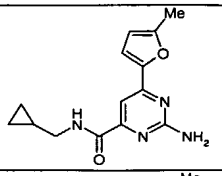
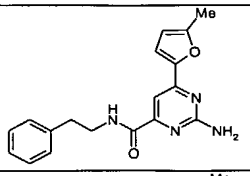
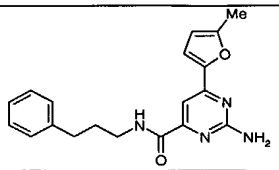
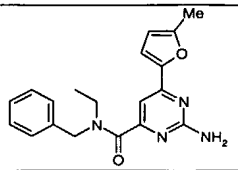
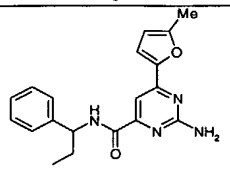
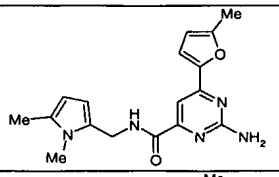
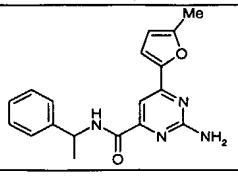
106		2-Amino-6-(2-furyl)-*N*-(2-indanyl)pyrimidine-4-carboxamide
107		2-Amino-6-(2-furyl)-*N*-(1*H*-imidazol-2-ylmethyl)pyrimidine-4-carboxamide
108		2-Amino-6-(2-furyl)-*N*-(1-*n*-propyl-1*H*-imidazol-2-ylmethyl)pyrimidine-4-carboxamide
109		2-Amino-*N*-(2-bromobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
110		2-Amino-*N*-(6-bromopyridin-2-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide
111		2-Amino-*N*-(6-aminopyridin-2-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide
112		2-Amino-6-(2-furyl)-*N*-(3-(1*H*-imidazol-1-yl)propyl)pyrimidine-4-carboxamide
113		2-Amino-6-(2-furyl)-*N*-(2-methoxyethyl-1*H*-imidazol-2-ylmethyl)pyrimidine-4-carboxamide
114		2-Amino-*N*-(1-ethyl-1*H*-imidazol-2-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide

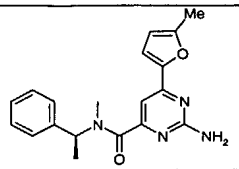
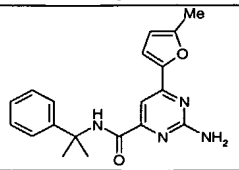
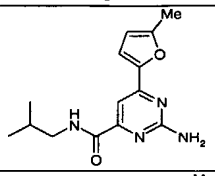
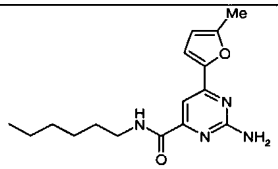
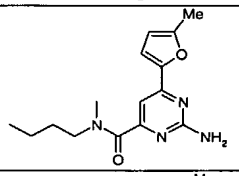
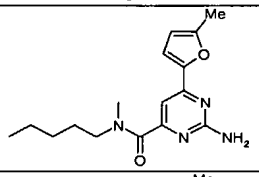
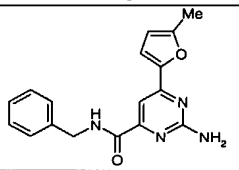
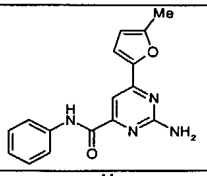
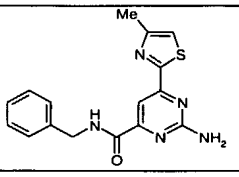
115		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl benzylcarbamate
116		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl cyclopentylcarbamate
117		6-(2-Amino-6-(2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl *n*-hexylcarbamate
118		2-Amino-*N*-(2-dimethylamino-6-methylpyridin-3-ylmethyl)-6-(2-furyl)pyrimidine-4-carboxamide
119		(R)-Methyl 2-(6-(2-amino-6-(2-furyl)pyrimidine-4-carboxamido))phenylacetate
120		(S)-Methyl 2-(6-(2-amino-6-(2-furyl)pyrimidine-4-carboxamido))phenylacetate
121		2-Amino-*N*-(2,6-dichlorobenzyl)-6-(2-furyl)pyrimidine-4-carboxamide
122		2-Amino-6-(2-furyl)-*N*-(6-methoxymethylpyridin-2-ylmethyl)-5-methylpyrimidine-4-carboxamide
123		2-Amino-*N*-(6-methoxymethylpyridin-2-ylmethyl)-6-(thiazol-2-yl)pyrimidine-4-carboxamide

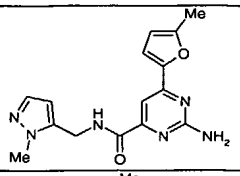
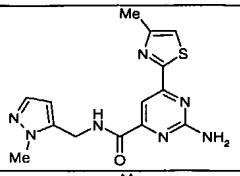
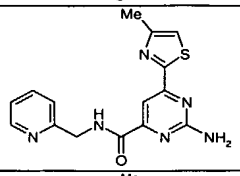
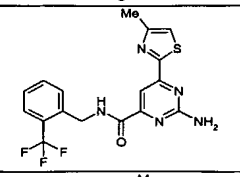
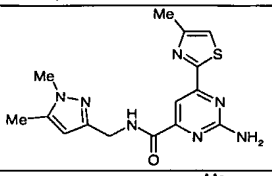
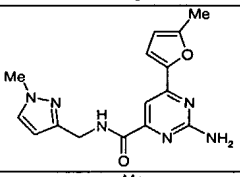
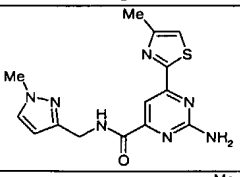
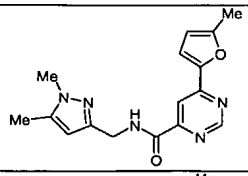
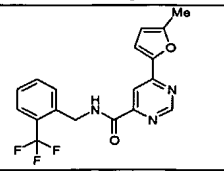
124		2-Amino-*N*-(3-methylpyridin-2-ylmethyl)-6-(thiazol-2-yl)pyrimidine-4-carboxamide
125		2-Amino-*N*-(6-*n*-propylpyridin-2-ylmethyl)-6-(thiazol-2-yl)pyrimidine-4-carboxamide
126		2-Amino-6-(5-methyl-2-furyl)-*N*-(2-trifluoromethylbenzyl)pyrimidine-4-carboxamide
127		2-Amino-6-(5-methyl-2-furyl)-*N*-(2-pyridylmethyl)pyrimidine-4-carboxamide
128		2-Amino-6-(5-methyl-2-furyl)-*N*-(1-methyl-1*H*-pyrrol-2-ylmethyl)pyrimidine-4-carboxamide
129		2-Amino-6-(5-methyl-2-furyl)-*N*-(6-methoxymethylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
130		6-(2-Amino-6-(5-methyl-2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl *tert*-butylcarbamate
131		6-(2-Amino-6-(5-methyl-2-furyl)pyrimidine-4-carboxamidomethyl)pyridin-2-ylmethyl morpholine-1-carboxylate
132		2-Amino-5-chloro-*N*-(6-methoxymethylpyridin-2-ylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide

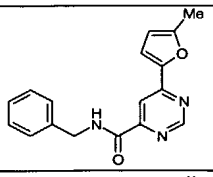
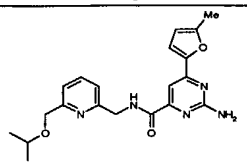
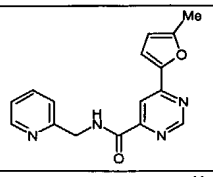
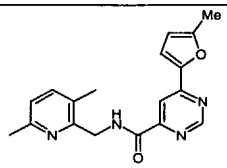
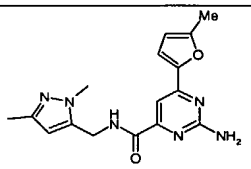
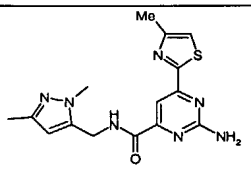
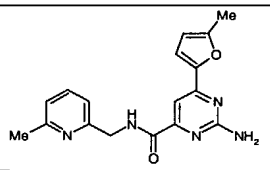
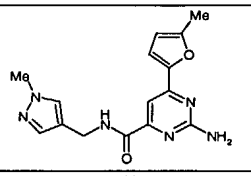
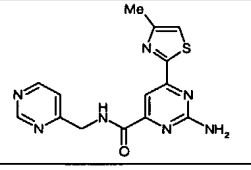
133		2-Amino-5-bromo-*N*-(6-methoxymethylpyridin-2-ylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
134		2-Amino-5-bromo-6-(5-methyl-2-furyl)-*N*-(2-trifluoromethylbenzyl)pyrimidine-4-carboxamide
135		2-Amino-*N*-(2-methylbenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
136		2-Amino-*N*-(3-methylbenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
137		2-Amino-*N*-(4-methylbenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
138		2-Amino-*N*-(2-chlorobenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
139		2-Amino-*N*-(3-chlorobenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
140		2-Amino-6-(5-methyl-2-furyl)-*N*-(3-pyridylmethyl)pyrimidine-4-carboxamide
141		2-Amino-6-(5-methyl-2-furyl)-*N*-(4-pyridylmethyl)pyrimidine-4-carboxamide

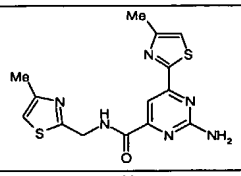
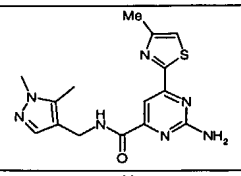
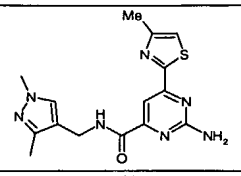
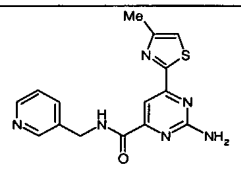
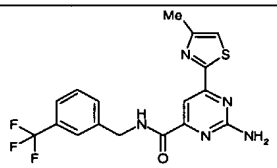
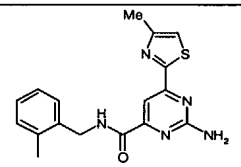
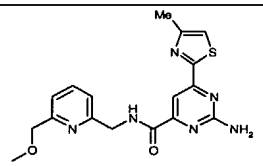
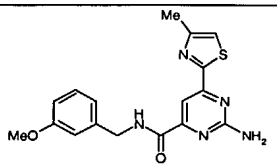
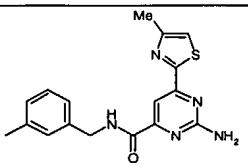
142		2-Amino-*N*-(2-methoxybenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
143		2-Amino-*N*-(3-methoxybenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
144		2-Amino-*N*-(3-fluorobenzyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
145		2-Amino-6-(5-methyl-2-furyl)-*N*-(3-trifluoromethylbenzyl)pyrimidine-4-carboxamide
146		2-Amino-6-(2-furyl)-*N*-(6-(triphenylmethoxymethyl)pyridin-2-ylmethyl)pyrimidine-4-carboxamide
147		2-Amino-6-(2-furyl)-*N*-(1-(2-(trimethylsilyl)ethoxy)methyl-1*H*-imidazole-2-ylmethyl)pyrimidine-4-carboxamide
148		2-Amino-6-(5-methyl-2-furyl)-*N*-(6-(*tert*-butyldimethylsilyloxymethyl)pyridin-2-ylmethyl)pyrimidine-4-carboxamide
149		2-Amino-*N*-(6-hydroxymethylpyridin-2-ylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
150		2-Amino-*N*-(1,5-dimethyl-1*H*-pyrazol-3-ylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide

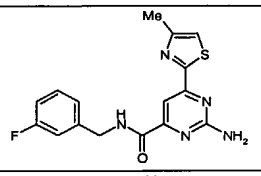
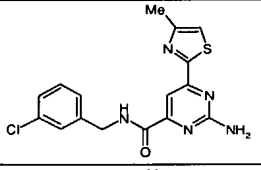
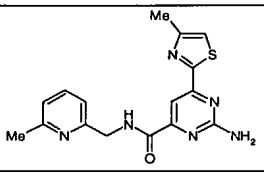
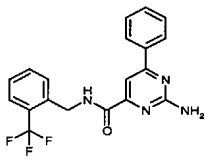
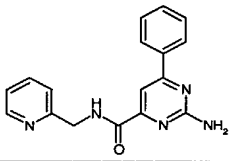
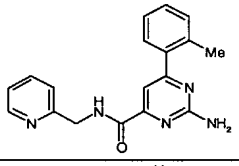
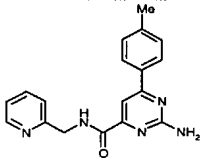
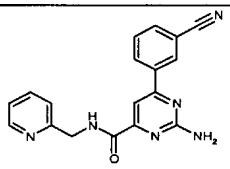
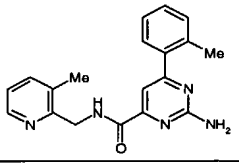
151		2-Amino-6-(5-methyl-2-furyl)-*N*-(5-methylisoxazol-3-ylmethyl)pyrimidine-4-carboxamide
152		2-Amino-6-(5-methyl-2-furyl)-*N*-(tetrahydrofuran-2-ylmethyl)pyrimidine-4-carboxamide
153		2-Amino-*N*-(cyclopropylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
154		2-Amino-6-(5-methyl-2-furyl)-*N*-(2-phenylethyl)pyrimidine-4-carboxamide
155		2-Amino-6-(5-methyl-2-furyl)-*N*-(3-phenylpropyl)pyrimidine-4-carboxamide
156		2-Amino-*N*-benzyl-*N*-ethyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
157		(R,S)-2-Amino-6-(5-methyl-2-furyl)-*N*-(1-phenylpropyl)pyrimidine-4-carboxamide
158		2-Amino-*N*-(1,5-dimethyl-1*H*-pyrrol-2-ylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
159		(R,S)-2-Amino-6-(5-methyl-2-furyl)-*N*-(1-phenylethyl)pyrimidine-4-carboxamide

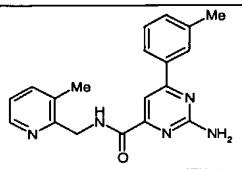
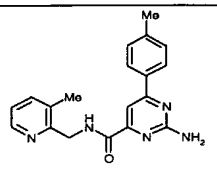
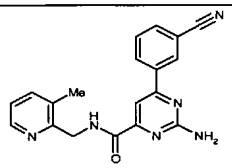
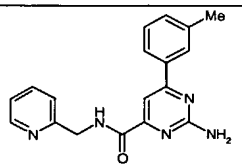
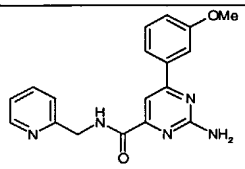
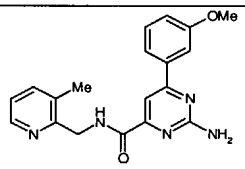
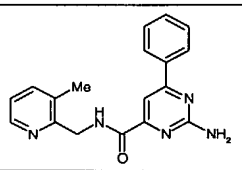
160		(S)-2-Amino-*N*-methyl-6-(5-methyl-2-furyl)-*N*-(1-phenylethyl)pyrimidine-4-carboxamide
161		2-Amino-6-(5-methyl-2-furyl)-*N*-(1-phenylprop-2-yl)pyrimidine-4-carboxamide
162		2-Amino-*N*-isobutyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
163		2-Amino-*N*-hexyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
164		2-Amino-*N*-butyl-*N*-methyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
165		2-Amino-*N*-methyl-6-(5-methyl-2-furyl)-*N*-pentylpyrimidine-4-carboxamide
166		2-Amino-*N*-benzyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
167		2-Amino-6-(5-methyl-2-furyl)-*N*-phenylpyrimidine-4-carboxamide
168		2-Amino-*N*-benzyl-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxamide

169		2-Amino-6-(5-methyl-2-furyl)-*N*-(1-methyl-1*H*-pyrazol-5-ylmethyl)pyrimidine-4-carboxamide
170		2-Amino-*N*-(1-methyl-1*H*-pyrazol-5-ylmethyl-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxamide
171		2-Amino-6-(4-methylthiazol-2-yl)-*N*-(pyridin-2-ylmethyl)pyrimidine-4-carboxamide
172		2-Amino-6-(4-methylthiazol-2-yl)-*N*-(2-trifluoromethylbenzyl)pyrimidine-4-carboxamide
173		2-Amino-*N*-(1,5-dimethyl-1*H*-pyrazol-3-ylmethyl)-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxamide
174		2-Amino-6-(5-methyl-2-furyl)-*N*-(1-methyl-1*H*-pyrazol-3-ylmethyl)pyrimidine-4-carboxamide
175		2-Amino-*N*-(1-methyl-1*H*-pyrazol-3-ylmethyl)-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxamide
176		*N*-(1,5-Dimethyl-1*H*-pyrazol-3-ylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
177		6-(5-Methyl-2-furyl)-*N*-(2-trifluoromethylbenzyl)pyrimidine-4-carboxamide

178		*N*-Benzyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
179		2-Amino-6-(5-methyl-2-furyl)-*N*-(6-(isopropyloxymethyl)pyridine-2-ylmethyl)pyrimidine-4-carboxamide
180		6-(5-Methyl-2-furyl)-*N*-(2-pyridylmethyl)pyrimidine-4-carboxamide
181		*N*-(3,6-Dimethylpyridin-2-ylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
182		2-Amino-*N*-(1,3-dimethyl-1*H*-pyrazol-5-ylmethyl)-6-(5-methyl-2-furyl)pyrimidine-4-carboxamide
183		2-Amino-*N*-(1,3-dimethyl-1*H*-pyrazol-5-ylmethyl)-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxamide
184		2-Amino-6-(5-methyl-2-furyl)-*N*-(6-methylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
185		2-Amino-6-(5-methyl-2-furyl)-*N*-(1-methyl-1*H*-pyrazol-4-ylmethyl)pyrimidine-4-carboxamide
186		2-Amino-6-(4-methylthiazol-2-yl)-*N*-(pyrimidin-4-ylmethyl)pyrimidine-4-carboxamide

187		2-Amino-6-(4-methylthiazol-2-yl)-*N*-(4-methylthiazol-2-ylmethyl)pyrimidine-4-carboxamide
188		2-Amino-*N*-(1,5-dimethyl-1*H*-pyrazol-4-ylmethyl)-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxamide
189		2-Amino-*N*-(1,3-dimethyl-1*H*-pyrazol-4-ylmethyl)-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxamide
190		2-Amino-6-(4-methylthiazol-2-yl)-*N*-(pyridin-3-ylmethyl)pyrimidine-4-carboxamide
191		2-Amino-6-(4-methylthiazol-2-yl)-*N*-(3-trifluoromethylbenzyl)pyrimidine-4-carboxamide
192		2-Amino-*N*-(2-methylbenzyl)-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxamide
193		2-Amino-*N*-(6-methoxymethylpyridin-2-ylmethyl)-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxamide
194		2-Amino-*N*-(3-methoxybenzyl)-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxamide
195		2-Amino-*N*-(3-methylbenzyl)-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxamide

196		2-Amino-*N*-(3-fluorobenzyl)-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxamide
197		2-Amino-*N*-(3-chlorobenzyl)-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxamide
198		2-Amino-*N*-(6-methylpyridin-2-ylmethyl)-6-(4-methylthiazol-2-yl)pyrimidine-4-carboxamide
199		2-Amino-6-phenyl-*N*-(2-trifluoromethylbenzyl)pyrimidine-4-carboxamide
200		2-Amino-6-phenyl-*N*-(pyridin-2-ylmethyl)pyrimidine-4-carboxamide
201		2-Amino-6-(2-methylphenyl)-*N*-(pyridin-2-ylmethyl)pyrimidine-4-carboxamide
202		2-Amino-6-(4-methylphenyl)-*N*-(pyridin-2-ylmethyl)pyrimidine-4-carboxamide
203		2-Amino-6-(3-cyanophenyl)-*N*-(pyridin-2-ylmethyl)pyrimidine-4-carboxamide
204		2-Amino-6-(2-methylphenyl)-*N*-(3-methylpyridin-2-ylmethyl)pyrimidine-4-carboxamide

205		2-Amino-6-(3-methylphenyl)-*N*-(3-methylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
206		2-Amino-6-(4-methylphenyl)-*N*-(3-methylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
207		2-Amino-6-(3-cyanophenyl)-*N*-(3-methylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
208		2-Amino-6-(3-methylphenyl)-*N*-(pyridin-2-ylmethyl)pyrimidine-4-carboxamide
209		2-Amino-6-(3-methoxyphenyl)-*N*-(pyridin-2-ylmethyl)pyrimidine-4-carboxamide
210		2-Amino-6-(3-methoxyphenyl)-*N*-(3-methylpyridin-2-ylmethyl)pyrimidine-4-carboxamide
211		2-Amino-*N*-(3-methylpyridin-2-ylmethyl)-6-phenylpyrimidine-4-carboxamide